Nickel-Catalyzed Coupling Reactions and Synthetic Studies toward *ent*-Dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

by

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Submitted to the Department of Chemistry
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To my family and David

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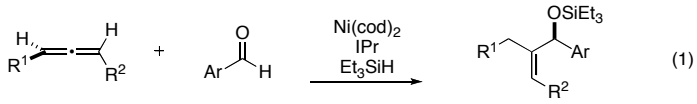
ABSTRACT

Nickel-Catalyzed Coupling Reactions

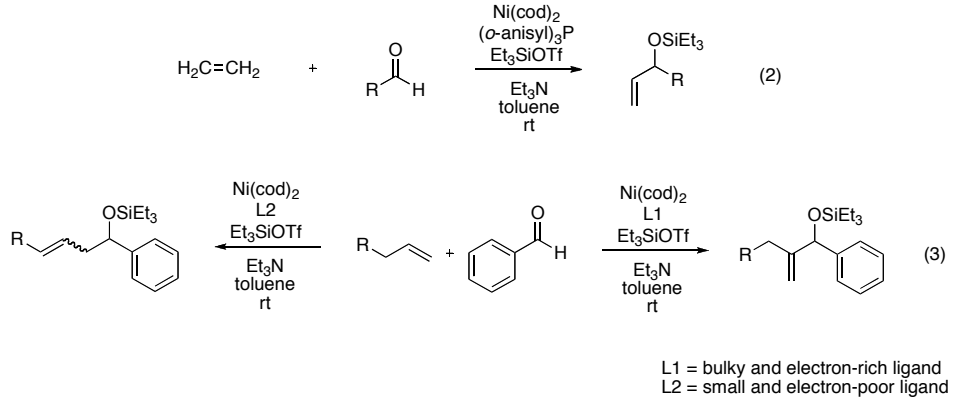
Nickel-catalyzed allene–aldehyde coupling and alkene–aldehyde coupling represent two methods of preparing allylic alcohols.

Most asymmetric transition metal-catalyzed methods of preparing enantiomerically enriched allylic alcohols rely on chiral ligands. The nickel-catalyzed allene–aldehyde coupling exploits the axial chirality in 1,3-disubstituted allenes in achieving asymmetric induction. When a chiral allene binds to a transition metal catalyst, the allene establishes a chiral environment around the metal center. This can possibly create a new stereocenter in a coupling product. Indeed, enantiomerically enriched allenes couple with aromatic aldehydes and triethylsilane in the presence of a nickel-carbene catalyst to provide selectively a *Z*-allylic alcohol with an enantiomeric excess identical to that of the starting chiral allene (eq 1).



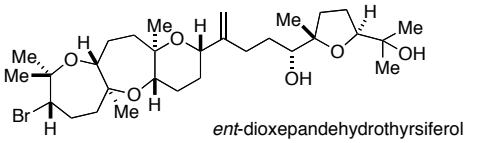
(1)

There is considerable interest to prepare allylic alcohols from simple alkenes because of their wide availability and ease of handling, as compare to alkenyl metal reagents, which are most commonly used to obtain allylic alcohols. It was reported in literature that a nickellacycle could be obtained from a mixture of nickel, α,ω-enal, and a silyl triflate. Under appropriate conditions β-hydride elimination could occur to provide an allylic alcohol product. The nickel(0) catalyst could be regenerated in the presence of a base. Ethylene and terminal alkenes are appropriate substrates for this transformation (eqs 2 and 3). Either allylic or homoallylic alcohol product can be obtained from terminal alkenes by using appropriate ligands for the nickel catalyst (eq 3).

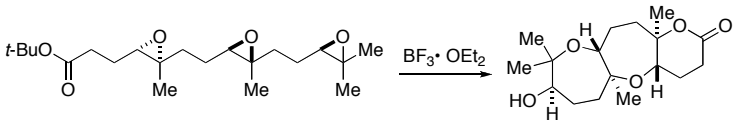


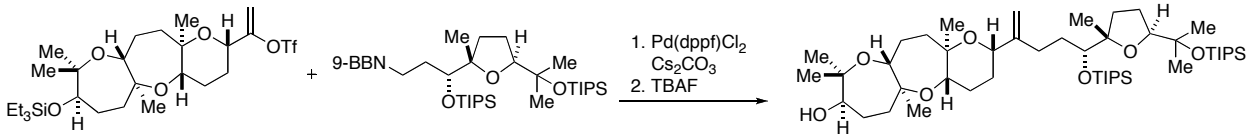
Synthetic studies of ent-dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

Dioxepandehydrothyrsiferol is a marine polycyclic ether natural product isolated from the red algae *Laurencia viridis*. Synthesis of the fused six-seven-seven cyclic ether in *ent*-dioxepandehdyrothyrsiferol through an epoxide-opening cascade strategy was explored. Formation of the strained tetrahydropyran ring in *ent*-dioxepandehdyrothyrsiferol directly from an epoxide-opening cascade of triepoxide allylic alcohol proved to be difficult. Alternatively, a δ-lactone was obtained using an epoxide-opening cascade of triepoxide *tert*-butyl ester. The furan side chain was installed via a Suzuki coupling.



ent-dioxepandehydrothyrsiferol





Thesis Supervisor: Timothy F. Jamison

Title: Associate Professor of Chemistry

PREFACE

Portions of this thesis have appeared in the following articles that were co-written by the author, and are reproduced in part with permission from:

Highly Enantioselective and Regioselective Nickel-Catalyzed Reductive Coupling of Allenes, Aldehydes and Silanes. Ng, Sze-Sze; Jamison, Timothy F. *J. Am. Chem. Soc*. **2005**, *127*, 7320–7321. Copyright 2005 American Chemical Society.

Enantioselective and Regioselective Nickel-Catalyzed Multicomponent Coupling of Chiral Allenes, Aromatic Aldehydes, and Silanes. Ng, Sze-Sze; Jamison, Timothy F. *Tetrahedron* **2005**, *61*, 11405–11417. Copyright 2005 Elsevier Science.

Simple Alkenes as Substitutes for Organometallic Reagents: Nickel-Catalyzed, Intermolecular Coupling of Aldehydes, Silyl Triflates, and Alpha Olefins. Ng, Sze-Sze; Jamison, Timothy F. *J. Am. Chem. Soc*. **2005**, *127*, 14194–14195. Copyright 2005 American Chemical Society.

Nickel-Catalyzed Coupling of Terminal Allenes, Aldehydes, and Silanes. Ng, Sze-Sze; Jamison, Timothy F. *Tetrahedron* **2006***, 62,* 11350–11359. Copyright 2006 Elsevier Science.

Nickel-Catalyzed, Carbonyl-Ene-Type Reactions: Selective for Alpha Olefins and More Efficient with Electron-Rich Aldehydes. Ho, Chun-Yu; Ng, Sze-Sze; Jamison, Timothy F. *J. Am. Chem. Soc.* **2006**, *128*, 5362–5363. Copyright 2006 American Chemical Society.

Nickel-Catalyzed Coupling of Alkenes, Aldehydes, and Silyl Triflates. Ng, Sze-Sze; Ho, Chun-Yu; Jamison, Timothy. F. *J. Am. Chem. Soc.* **2006**, *128*, 11513–11528. Copyright 2006 American Chemical Society.

Part of the nickel-catalyzed alkene–aldehyde coupling was contributed by Dr. Chun-Yu Ho.

Part of the synthesis of *ent*-dioxpendehydrothyrsiferol was contributed by Jessica Tanuwidjaja.

X-ray crystal structure data was collected by Dr. Peter Müller.

ORTEP diagrams were generated by Dr. David Laitar.

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Five years in graduate school have gone by quickly, I owe the following people who trained me to be an organic chemist.

Working with Professor Bimal Banik was my first opportunity to connect textbook chemistry to real synthetic problem in the laboratory and he sparked my interest in organic chemistry.

Professor Michael Krische was my inspiring undergraduate research advisor whom I admired and I always think of him as one of my role models.

Professor Timothy Jamison influenced me most as my academic and career advisor. He has been very liberal and always encouraging in letting me explore my projects in anyway I determined reasonable. My ideas were not always bright but he always provided guidance when I needed it. One most important lesson I learnt working with Tim was to be objective and not to give up easily. Try everything possible and anything that seemed unlikely but somehow still have 1% chance that it would work. Never assume a theory was wrong until proven by an experiment. Tim was also kind and funny. Every once in a while he would have a comment that made my day. He also cared very much about my career development. He has given me every opportunity to meet and talk to chemists working in industry through fellowship conferences.

In Tim's lab I also had the opportunity to learn from skillful senior chemists (Carmela Molinaro, Johann Chan, Betsy Colby, Tim Heffron, Karen Miller, Sejal Patel, Chudi Ndubaku, Ryan Moslin, Neil Langille, Jason Ho and others). Their experience and tricks were passed along to others and me and will be passed along for generations of chemists to come in Tim's lab.

Professor Gregory Fu and Professor Mohammad Movassaghi were both insightful and provided honest opinions and suggestions for my thesis over the years.

I also had the opportunity to work with Jason Chun-Yu Ho, who is now a professor in the Chinese University of Hong Kong. I have learnt a great deal of practical organic chemistry skills from him. He has contributed immensely in the development of nickel-catalyzed coupling of alkenes and aldehydes and has provided insightful interpretation of experimental data. I also want to mention that he is a true master of column chromatography.

And to all of you working with me in the lab (Jeff Byers, Lucas Brändli, Victor Gehling, Andrew Lauer, Aaron Van Dyke, Kristin Schleicher, Brian Underwood, Ivan Vilotijevic, Chris Morten, Jessica Tanuwidjaja, Brian Sparling, and Ngan Nguyen). Even though most of you do not work in my project you have helped by giving me constructive comments throughout the way. Jokes and all the mess-ups we came up with every day were part of my experience to become a better chemist! I also wish Jessica success in her upcoming projects after working with me for one semester. She has been careful and productive in her work and has made significant contribution to our project.

To my family, their financial support for my education was a tremendous help. They also taught me to be independent. And David Laitar, from whom I found companionship and

happiness when I was in graduate school. He has brought me excitement every day. David is also a gifted chemist; I admire his intellect and his dedication to perfection in everything he does.

TABLE OF CONTENTS

ABBREVIATIONS

Ac	acetyl
Acac	acetoacetate
Anis	anisyl (methoxy-phenyl)
Ar	aryl
atm	atmospheres
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxy carbonyl
BRSM	based on recovered starting material
Bu	butyl
°C	degree (Celsius)
cat.	catalytic
cod	cyclooctadiene
COSY	correlated spectroscopy
Cp	cyclopentadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cyp	cyclopentyl
δ	chemical shift in parts per million
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DET	diethyltartrate
DHF	dihydrofuran
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMM	dimethoxymethane
DMP	Dess Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESI	electron spray ionization
Et	ethyl
Et_3B	triethylborane
EtO	ethyoxy
Et_2O	diethylether
EtOAc	ethyl acetate

eq	equation
Fc	ferrocenyl
g	grams
GC	gas chromatography
h	hours
Hept	heptyl
Hex	hexyl
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
I-BBN	9-iodo-9-borabicyclo[3.3.1]nonane
i-Pr	isopropyl
IPr	bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
L	liters
L_n	ligand (n = number)
LHMDS	lithium hexamethyldisilazide
m	meta
m	milli
μ	micro
M	molar
Me	methyl
MeO	methoxy
MeOH	methanol
Mes	mesityl
MHz	megahertz
min	minutes
mol	moles
Ms	mesyl
n	normal
NHC	*N*-heterocyclic carbene
Ni	nickel
NMDPP	neomenthyldiphenylphosphine
NMR	nuclear magnetic resonance
n.d.	not determined
nOe	nuclear Overhauser effect
NOSEY	nuclear Overhauser effect spectroscopy
o	ortho
Oct	octyl
p	para
Pent	pentyl
Ph	phenyl
PPTS	pyridinium *para*-tolulenesulfonate
Pr	propyl
Pybox	pyridinebis(oxazoline)

Pyr	pyridine
R	any substituents
sat.	saturated
SiO_2	silica gel
t_R	retention time
t-Bu	*tert*-butyl
temp	temperature
TMS	trimethylsilyl
TBS	*tert*-butyl dimethylsilyl
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
Ts	tosyl
TsOH	*para*-toluenesulfonic acid
wt	weight

Chapter 1

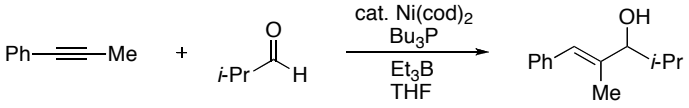
Nickel-Catalyzed Reductive Coupling of Allenes and Aldehydes

Introduction

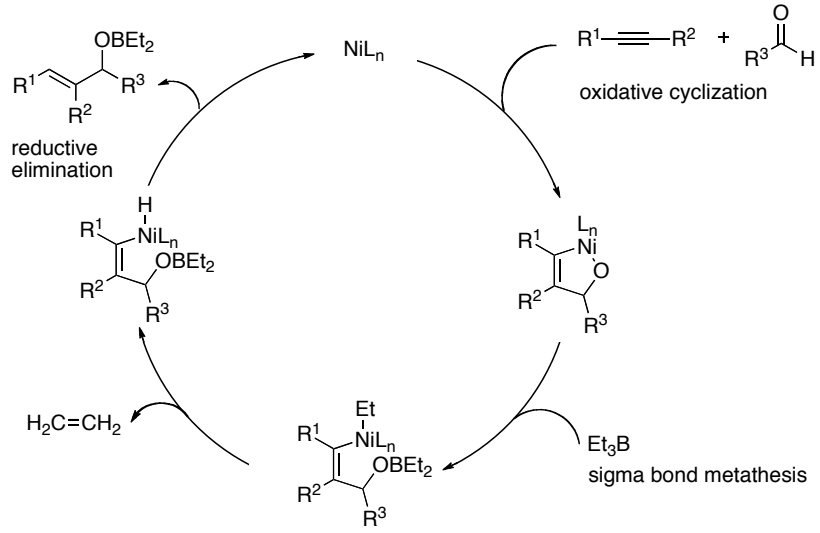
Nickel-Catalyzed Reductive Coupling Reactions

While palladium is far more popular than nickel in cross coupling reactions such as Suzuki coupling, nickel is more often used in the intermolecular coupling of two different unsaturated functional groups (such as an alkyne and an aldehyde) in the presence of a reducing agent (reductive coupling, Scheme 1).[1,2] In the presence of a catalytic amount of nickel and a reducing agent, a carbon–carbon bond is formed between an electron-rich component (e.g. alkyne, 1,3-enyne, 1,3-diene, allene, etc.) and an electrophilic component (e.g. aldehyde, epoxide, enone, etc.). Some of these couplings are summarized in Table 1. A commonly proposed mechanism for these reductive couplings involves oxidative cyclization, sigma bond metathesis, and reductive elimination (Scheme 1).

Scheme 1

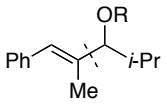
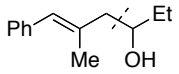
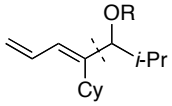
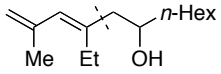
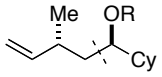


proposed catalytic cycle:



These nickel-catalyzed coupling reactions have advantages over existing methods. In a single operation simple functional groups such as an alkyne are added directly to an electrophile. This one-step protocol is more convenient as compared to a more traditional approach, which would involve hydrometallation of an alkyne followed by addition of the alkenyl metal to an aldehyde.[3] The nickel-catalyzed reductive coupling approach is also generally more convenient than preparing the corresponding Grignard reagent and adding it to the desired electrophiles. Finally, the use of nickel in the presence of a chiral ligand also provides enantiomerically enriched coupling product in many cases.[2d, 2e, 2g, 2k, 2m]

Table 1. Examples of Nickel-Catalyzed Reductive Coupling Reactions

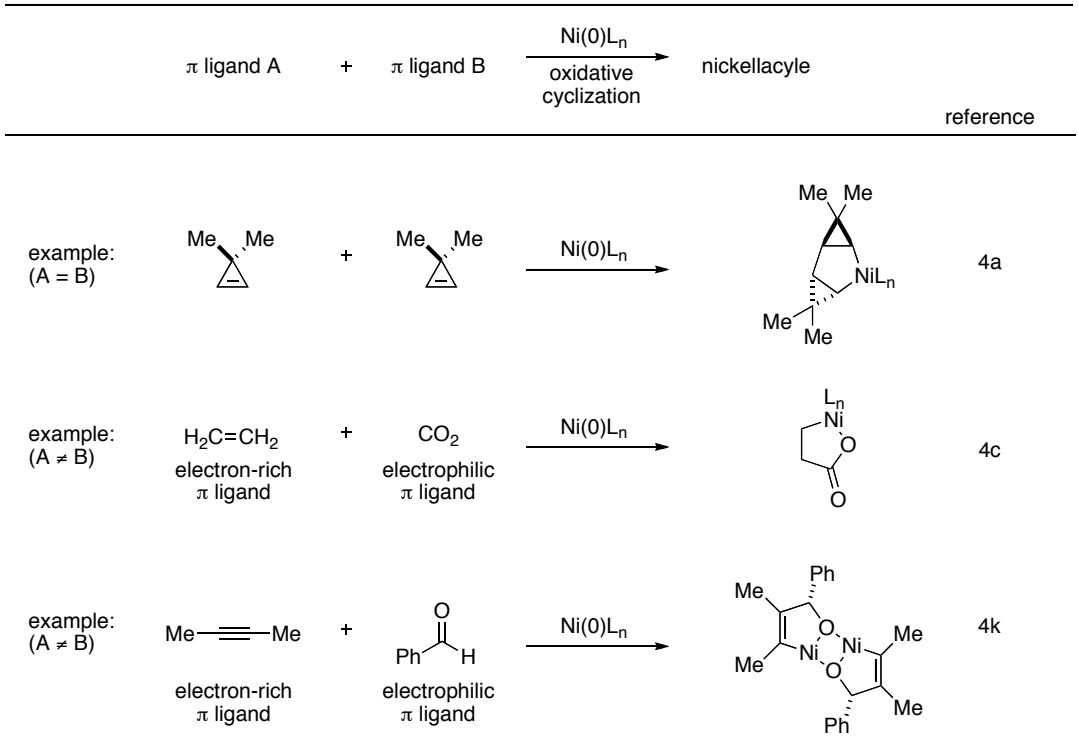
electron-rich function group	electrophilic functional group	reducing agent	product example[a]	reference[b]
alkyne	aldehyde	Et_3B		2c, 2d*, 2e*
"	"	Et_3SiH		2f, 2g*
"	"	$CrCl_2$		2h
"	epoxide	Et_3B		2i
1,3-enyne	aldehyde	Et_3B		2j, 2k*
"	epoxide	Et_3B		2j
1,3-diene	aldehyde	Et_2Zn		2l
"	"	Et_3B		2l
"	"	Et_3SiH		2l, 2m*

[a] Dashed line indicates the site of carbon–carbon bond formation. [b] asterisk indicates a reference to the asymmetric version.

Proposed Nickellacycle Intermediate in Nickel-Catalyzed Reductive Coupling Reactions

A commonly proposed mechanism for nickel-catalyzed reductive couplings involves a nickellacycle intermediate (Scheme 1).[2] A nickellacycle can be obtained from oxidative addition of two π ligands to a Ni(0) species (Scheme 2).[4,5] This step is termed oxidative cyclization or oxidative coupling. Oxidative cyclization can occur between two identical π ligands or two different π ligands.[4] For example, two cyclopropenes can add to nickel to form a nickellacyclopentane.[4a] Coupling of 1:1 mixture of ethylene and carbon dioxide with nickel afforded a nickellalactone.[4c] Coupling of butyne and benzaldehyde yielded a nickelladihydrofuran.[4k] Nickellacycle formation is a fundamental concept in nickel chemistry and has been proposed in many nickel-catalyzed reactions. Examples are [2+2] cycloaddition of alkene,[7] cyclotrimerization of alkyne,[8] as well as nickel-catalyzed reductive coupling reactions.[2]

Scheme 2



In the case of a nickel-catalyzed reductive coupling, the proposed oxidative cyclization step typically involves oxidative addition of an electron-rich π component (e.g. alkyne, enyne, allene, etc.) and an electrophilic π component (e.g. aldehyde, enone, carbon dioxide etc.) and would result in a Ni(II) nickellacycle intermediate.[2] To regenerate the Ni(0) catalyst the Ni(II) nickellacycle needs to be reduced. Nickellacycle is known to undergo reactions such as β-hydride elimination, reductive elimination, and sigma bond metathesis (see Scheme 1 for an example).[4k,6] In a typically proposed mechanism of nickel-catalyzed reductive coupling, formation of nickellacycle is always followed by a sigma bond metathesis. Triethylborane, alkylsilanes, and diethylzinc are the most common reagents to promote sigma bond metathesis in nickel-catalyzed reductive coupling.[2] Study by Mori and Sato on their nickel-catalyzed coupling of 1,3-dienes and aldehydes supported this mechanism.[6f,6g] Ogoshi has recently isolated a nickelladihyrofuran from an oxidative cyclization of nickel with butyne and benzaldehyde (Scheme 2).[4k] This nickelladihydrofuran could be reduced by dimethylzinc to yield a butyne–benzaldehyde reductive coupling product, again consistent with the standard proposed mechanism.

Transition-Metal Catalyzed Allene–Aldehyde Couplings.

Prior to our studies, the majority of intramolecular and intermolecular reactions of simple allenes and aldehydes involved the union of one of the sp^2-hybridized carbons of the allene with the carbonyl group of the aldehyde, affording homoallylic alcohols in the case of multi-component coupling reactions[9,10,11] and, in allenylmetal addition reactions, homopropargylic alcohols.[12] With enantiomerically enriched allenylmetal reagents, enantiomerically enriched homopropargylic alcohols can be obtained.[12c,12d] Highly enantioselective transition metal-

catalyzed coupling of simple unactivated allenes with aldehydes was not available. Only one attempt has been reported, with enantiomeric excess less than 24%.[10c,10i]

Our nickel-catalyzed allene–aldehyde coupling is unique from existing methods and addressed the enantioselectivity problems as mentioned above. Enantiomerically enriched allylic alcohols were obtained with the same enantiomeric excess as the starting allenes via a chirality transfer process.[13,14]

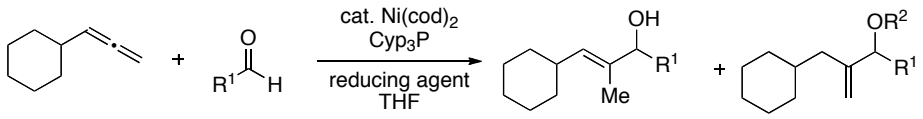
Evaluation of Experimental Parameters.

Triethylborane (Et_3B) and alkylsilanes are functional group-tolerant reducing agents in several nickel-catalyzed reactions, such as reductive coupling reactions of a diene, an alkyne, or an enyne with an aldehyde, ketone, or epoxide.[2] Thus the development of a reductive coupling reaction between an allene and an aldehyde commenced with evaluation of these reducing agents. A mixture of cyclohexylallene (**1a)**, aldehyde, $Ni(cod)_2$, tricyclopentylphosphine, and a reducing agent provided two major coupling products **2** and **3** (Table 2).

The nickel-catalyzed allene–aldehyde coupling displayed reducing agent-dependent regioselectivity. With triethylborane as the reducing agent, allylic alcohol **2a** predominated over **3a** in the coupling of allene **1a** and isobutyraldehyde (Table 2, entry 1). Switching the reducing agent from triethylborane to triethylsilane (Et_3SiH) afforded geminally disubstituted allylic ether (**3b**) as the exclusive three-component coupling product, along with products corresponding to hydrosilylation of the allene (entry 2). Trisubstituted allylic ether **2b** was not observed in the NMR spectrum of the crude reaction mixture. Several commercially available silanes were examined next. *tert*-Butyldimethylsilane (*t*-$BuMe_2SiH$) provided a similar yield of **3c** (entry 3). Triisopropylsilane (*i*-Pr_3SiH) afforded **3d** only upon heating (entry 4). Under similar conditions

other common silanes did not provide **3** in significant yields.[15] Since regioselectivity was excellent with a silane as the reducing agent, alkylsilanes were used in further evaluation of the nickel-catalyzed allene–aldehyde coupling.

Table 2. Reducing Agent-Dependent Regioselectivity



1a **2** **3**

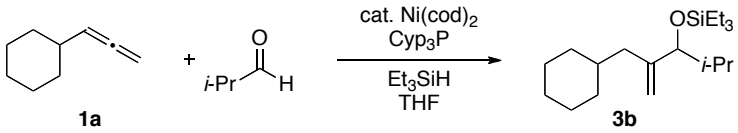
entry	reducing agent	R^1	yield (%)[a,b]	**2**:**3**
1[c]	Et_3B	*i*-Pr	50	89:11 (R^2 = H) (**2a**:**3a**)
2	Et_3SiH	*i*-Pr	51	5:95 (R^2 = Et_3Si) (**2b**:**3b**)
3[d]	*t*-$BuMe_2SiH$	*i*-Pr	53	5:95 (R^2 = *t*-$BuMe_2Si$) (**2c**:**3c**)
4[e,f]	*i*-Pr_3SiH	Cy	24	5:95 (R^2 = *i*-Pr_3Si) (**2d**:**3d**)

[a] General procedure: To a solution of $Ni(cod)_2$ (10 mol%) and Cyp_3P (10 mol%) were added the reducing agent (200 mol%) and the aldehyde (200 mol%). Allene **1a** (100 mol%) in THF was added to the reaction mixture over 8 to 12 h. The reaction mixture was stirred 18 h at room temperature. [b] Isolated yield. [c] $Ni(cod)_2$ (20 mol%) and Cyp_3P (40 mol%) were used. [d] Cyp_3P (20 mol%) were used. [e] The reaction was heated to 50 °C in toluene. [f] 300 mol% of reducing agent was used.

Solvent and ligand effects were briefly examined in the nickel-catalyzed coupling of allene **1a** and isobutyraldehyde (Table 3). While toluene, ethyl acetate (EtOAc), and methanol (MeOH) could also be used (entries 4-8), tetrahydrofuran (THF) was the most suitable solvent for this coupling reaction (entries 2-3). The nickel/ligand ratio was also found to be an important variable. The reductive coupling afforded less than 5% allylic ether **3b** without a supporting ligand (entry 1). A 1:1 ratio of $Ni(cod)_2$ and tricyclopentylphosphine (Cyp_3P) was optimal, regardless of the choice of solvent (entries 2, 4, 6, 8). Only bulky, electron-rich, and monodentate phosphines such as Cyp_3P and Cy_3P were compatible ligand for the nickel-catalyzed allene–aldehyde coupling. Smaller and bidentate phosphines afforded only a trace amount of coupling products.[16] The *N*-heterocyclic carbene IPr, which is also a bulky and

electron rich monodendate ligand, was also an excellent ligand but only with aromatic aldehydes (vide infra). The yield of the coupling product could be increased further simply by using a greater amount of aldehyde and silane (Table 4).

Table 3. Evaluation of Solvents and Ligand Ratios

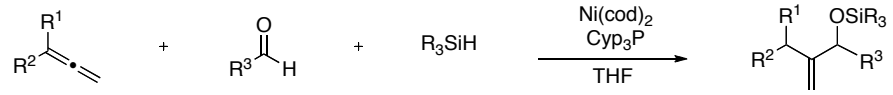


1a **3b**

entry	ligand (mol%)	solvent	yield (%) [a, b]
1	none	THF	<5
2	10	THF	51
3	20	THF	50
4	10	EtOAc	40
5	20	EtOAc	21
6	10	MeOH	36
7	20	MeOH	27
8	10	toluene	46

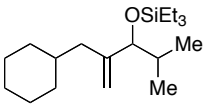
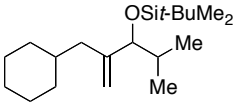
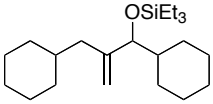
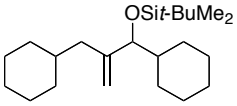
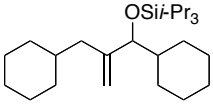
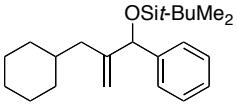
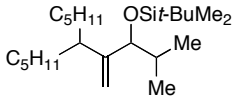
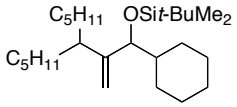
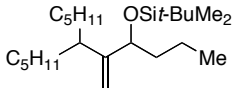
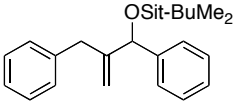
[a] General procedure: To a solution of $Ni(cod)_2$ (10 mol%) and Cyp_3P were added Et_3SiH (200 mol%) and the aldehyde (200 mol%). Allene **1a** (100 mol%) in THF was added to the reaction mixture over 4 h. The reaction mixture was stirred 18 h at room temperature. [b] Isolated yield.

Table 4. Nickel-Catalyzed Reductive Coupling of Terminal Allenes with Aldehydes



3

1a: R^1 = Cy, R^2 = H
1b: R^1 = R^2 = *n*-C_5H_{11}
1c: R^1 = Ph, R^2 = H

entry	allene	aldehyde	silane	product		yield (%) [a,b]
1	**1a**	*i*-Pr	Et_3SiH		**3b**	52
2	"	"	*t*-$BuMe_2SiH$		**3c**	71
3	"	Cy	Et_3SiH		**3e**	46
4	"	"	*t*-$BuMe_2SiH$		**3f**	73
5	"	"	*i*-Pr_3SiH		**3d**	24 [c]
6	"	Ph	*t*-$BuMe_2SiH$		**3g**	86 [d]
7	**1b**	*i*-Pr	*t*-$BuMe_2SiH$		**3h**	75
8	"	Cy	"		**3i**	68
9	"	*n*-Bu	"		**3j**	35
10	**1c**	Ph	"		**3k**	56 [d] (5) [e]

[a] General procedure: See experimental section. [b] Isolated yield. [c] Heated to 50 °C in toluene. [d] Cyp_3P was replaced by IPr. [e] Cyp_3P was employed as the ligand. Yield was determined by NMR of the crude mixture versus DMF as an external standard.

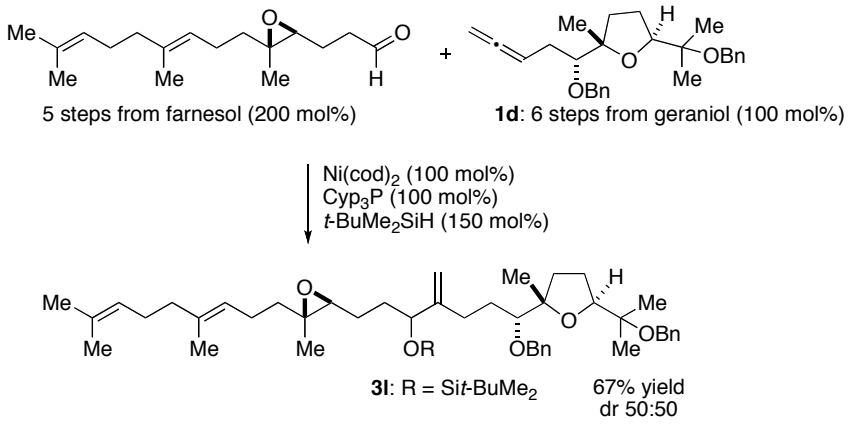
The scope of nickel-catalyzed reductive coupling of allenes and aldehydes was also evaluated. The catalyst system derived from $Ni(cod)_2$ and Cyp_3P promoted the coupling of allenes **1a**, **1b** and **1c** with various aliphatic aldehydes in good yield and excellent regioselectivity when a trialkylsilane (Et_3SiH or *t*-$BuMe_2SiH$) was employed as a reducing agent (Table 4). In all cases, carbon–carbon bond formation occurred at the sp–hybridized carbon (rather than the sp^2–hybridized carbons) of the allenes (regioselectivity). Homoallylic alcohol products were not observed in any case. The more hindered double bond reacted with the aldehyde, rather than the less substituted double bond in all cases as well (entries 1-10). This site selectivity was not affected by the steric bulk around the allene. Allene **1b**, possessing two geminal alkyl substituents, also underwent coupling with aliphatic aldehydes with the same sense of site selectivity as **1a** and **1b** (Table 3, entries 7–9).

The size of the silane affected the yield of the coupling product significantly. Switching from *t*-$BuMe_2SiH$ to Et_3SiH lowered the yield substantially (Table 3, entries 1–4) due to competing hydrosilylation of the allene; more hydrosilylation of allene was observed in the latter case. This phenomenon might be related to the relative size of those two organosilanes. Triisopropylsilane (*i*-Pr_3SiH), however, appeared to be too bulky for either the coupling or hydrosilylation to occur efficiently (entry 5).

Coupling of allene **1a** and **1c** with aromatic aldehyde such as benzaldehyde proceeded with higher yield when IPr was used as ligand instead of Cyp_3P (entries 6, 10). *N*-heterocyclic carbene IPr also seemed to limit oligomerization of allene better than Cyp_3P. With Cyp_3P as the supporting ligand, oligomerization of **1c** was pronounced, and **3k** was obtained in only 5% yield (entry 10). Nevertheless, this problem was alleviated when Cyp_3P was replaced by IPr (entry 10), and the same regioselectivity and site selectivity was observed as with Cyp_3P.

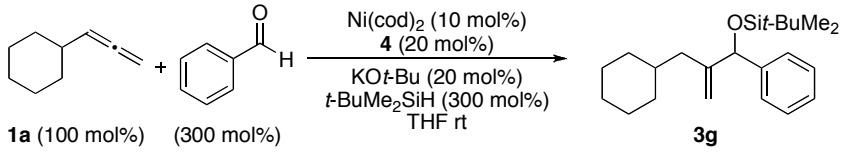
The nickel-catalyzed reductive coupling of allenes and aldehydes provides a method for obtaining allylic alcohols that complements Grignard reactions between alkenyl magnesium halides and aldehydes. One example clearly demonstrated this feature of the nickel-catalyzed coupling was the synthesis of epoxy allylic alcohol **3l** (Scheme 3).[17a] It was reported by Forsyth that γ-epoxy aldehyde cannot react with propenyl magnesium bromide to yield the corresponding allylic alcohol product.[17b] On the other hand, γ-epoxy aldehyde derived from farnesol coupled with allene **1d** to provide epoxy allylic ether **3l** in reasonable yield when a stoichiometric amount of nickel was used.[17c]

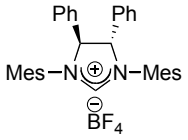
Scheme 3



A few chiral ligands (**4a**-**4e**) were evaluated for enantioselectivity in the nickel-catalyzed allene–aldehyde coupling (Scheme 4). In the coupling of cyclohexylallene and benzaldehyde, chiral *N*-heterocyclic carbenes **4a** and **4b** provided good yield of coupling product **3g** but in no cases were enantiomeric excess more than 24%. Since the catalyst control strategy did not provide good asymmetric induction, focus was directed to a substrate control strategy. 1,3-disubstituted allenes are axially chiral. Chirality transfer from chiral allene to the product might be possible in the nickel-catalyzed allene–aldehyde coupling.

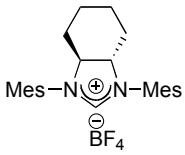
Scheme 4





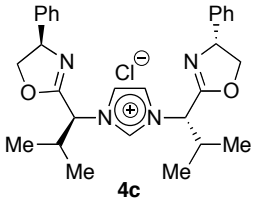
4a

86% yield
24% ee



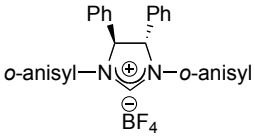
4b

81% yield
< 5% ee



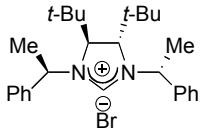
4c

< 5% yield



4d

< 5% yield



4e

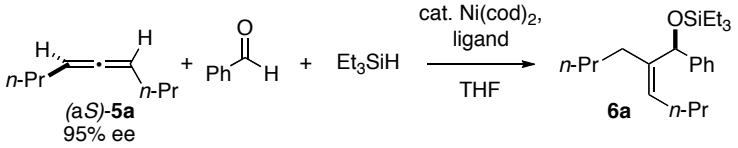
< 20% yield

Enantiomerically enriched 1,3-disubstituted allene (a*S*)-4,5-nonadiene (**5a**, 95% ee) was chosen as the first substrate to study the chirality transfer process in the nickel-catalyzed allene–aldehyde coupling. (a*S*)-4,5-nonadiene (**5a**) has the same substituent at both ends of the allene, therefore minimizing the number of possible coupling products. It was readily prepared in enantiomerically enriched form from the corresponding enantiomerically enriched propargyl alcohol.[18]

A ligand-dependent chirality transfer process was observed in the nickel-catalyzed reductive coupling of (a*S*)-4,5-nonadiene (**5a**) and benzaldehyde (Table 5). Using standard coupling conditions developed for terminal allenes, enantiomerically enriched **5a** coupled with benzaldehyde to afford product **6a** in 77% yield and with >95:5 *Z*/*E* selectivity (Table 5, entry 1).

However, while the starting allene had an enantiomeric excess (ee) of 95%, the ee of the product in the coupling reaction was substantially lower (62%). We thus conducted another evaluation of supporting ligands in this transformation with the aim of finding one that was not only efficacious, but also transferred the axial chirality of the allene to the product to a greater extent than Cyp_3P did. *N*-heterocyclic carbene IPr provided a solution to the erosion of enantiomeric purity that we observed using Cyp_3P (entries 2-7).

Table 5. Ligand-Dependent Chirality Transfer



entry	ligand	yield **6a** (%) [a,b]	ee (%)
1[c]	Cyp_3P	77	62
2	IPr	78	95
3	IPrHCl, Cs_2CO_3	65	23
4	IPrHCl, KO*t*-Bu	71	95
5	SIPrHBF$_4$, KO*t*-Bu	36	95
6[d]	IPr	88	95
7[d]	IPr	80[e]	95

[a] General procedure: To a solution of $Ni(cod)_2$ (20 mol%) and ligand (40%) were added Et_3SiH (300 mol%) and the aldehyde (300 mol%). Allene **5a** (100 mol%) in THF was added to the reaction mixture over 4.5 h. The reaction mixture was stirred 8 h at room temperature. [b] NMR yield versus DMF as an external standard. In all cases, the *Z*/*E* selectivity was >95:5 (^{1}H NMR of unpurified reaction mixture). [c] 20 mol% Cyp_3P was used. [d] Allene **5a** was added at –78 °C in one portion, and the mixture was allowed to warm to ambient room temperature. [e] Isolated yield of **6a**.

The method of generating the catalytically competent ligand (the "free carbene") from an imidazolium salt precursor had significant effects on both yield and the degree of chirality transfer (Table 5, entries 2-5). In all cases in which the free carbene was generated in situ (entries

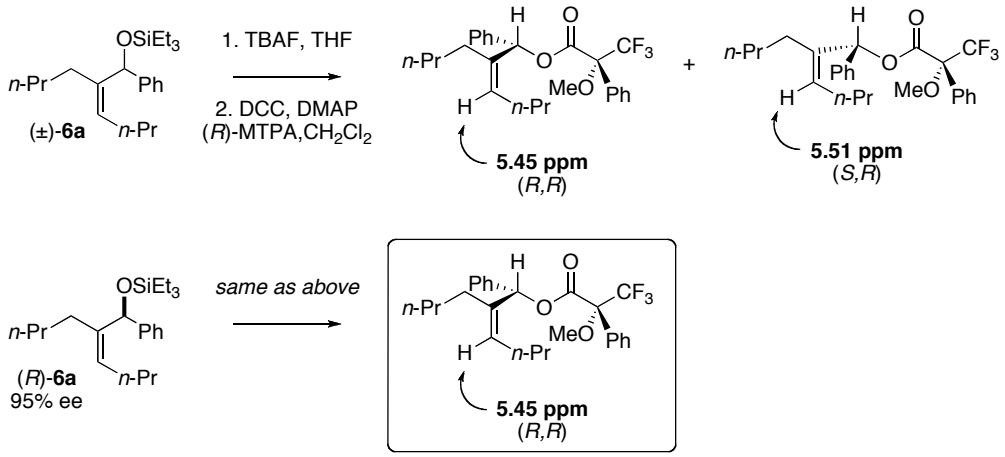
3-5), either the yield or ee of the product was lower than that obtained with Cyp_3P (entry 1). However, using of the free carbene IPr itself afforded the product in near identical yield as Cyp_3P and with complete transfer of chirality, giving product of 95% ee (entry 2).

Slow addition of the allene to the other components of the reaction in THF at ambient room temperature was used during the early stages of development of this transformation in order to minimize side reactions involving allene–allene coupling (Table 5, entries 1-5). We later found that these byproducts were suppressed by adding the allene to the reaction mixture at reduced temperature (–78 °C). The need for slow addition was thus obviated, and this modification also resulted in a further increased yield (Table 5, entries 6-7).

With the use of an NHC ligand, homoallylic products arising from reaction of the benzaldehyde at the sp^2 carbons of the allene **5a** could be detected in the unpurified reaction mixtures (^{1}H NMR). In the case at hand, the ratio of the allylic product to the sum of all homoallylic products was nevertheless still rather high (94:6). The latter were removed by straightforward column chromatography (SiO_2).

The configuration of allylic ether **6a** was determined by a Mosher's ester analysis (Scheme 5).[19] Removal of the Et_3Si group (TBAF/THF) from racemic **6a** and esterifying with the *R* enantiomer of the Mosher acid provided a mixture of two diastereomeric esters. This sequence was repeated with the 95% ee product. ^{1}H NMR analysis of both products indicated that the vinylic proton of the major diastereomer of the ester formed using the enantiomerically enriched material was upfield (5.45 ppm) relative to that of the minor diastereomer (5.51 ppm). These results suggested that the configuration of the product **6a** from the nickel-catalyzed coupling of (a*S*)-allene **5a** and benzaldehyde was *R*.

Scheme 5



With reaction conditions in hand that provided a good chemical yield of highly enantiomerically enriched material in the multicomponent coupling reaction, the scope of this novel transformation was examined (eq 1 and Table 6). In all cases examined, the degree of chirality transfer was 100%, and the *Z*/*E* selectivity was uniformly >95:5.

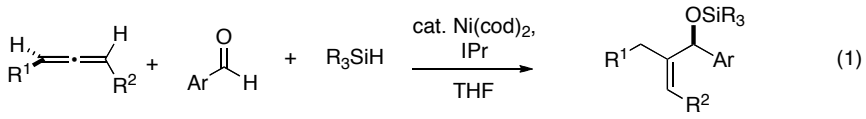
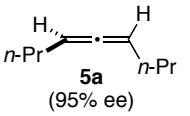
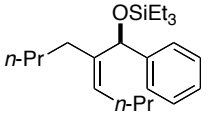
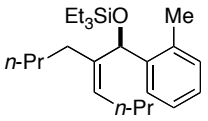
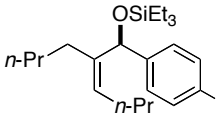
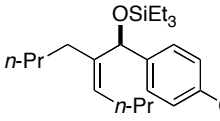
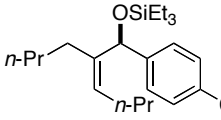
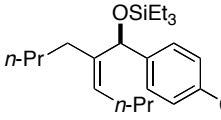
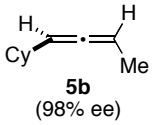
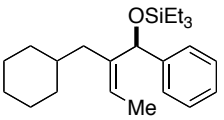
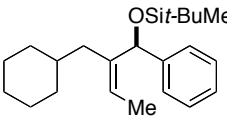
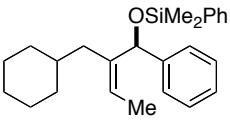
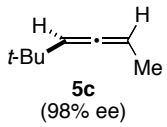
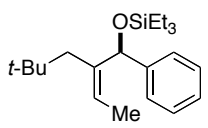


Table 6. Nickel-Catalyzed Coupling of Chiral Allenes and Aldehydes[a]

entry	allene	product	allylic: homoallylic [b,c]	yield (allylic), [d] *Z* / *E* [c]	site selectivity [c]	ee (%) [e]
1	 **5a** (95% ee)	 **6a**	94:6	80%, >95:5	n.a.	95
2	**5a**	 **6b**	90:10	70%, >95:5	n.a.	95
3	**5a**	 **6c**	95:5	74%, >95:5	n.a.	95
4	**5a**	 **6d**	93:7	75%, >95:5	n.a.	95
5	**5a**	 **6e**	90:10	56%, >95:5	n.a.	95
6 [f]	**5a**	 **6f**	90:10	66%, >95:5	n.a.	95
7	 **5b** (98% ee)	 **6g**	93:7	76%, >95:5	>95:5	98
8	**5b**	 **6h**	90:10	68%, >95:5	>95:5	98
9	**5b**	 **6i**	93:7	65%, >95:5	>95:5	98
10	 **5c** (98% ee)	 **6j**	85:15	40%, >95:5	>95:5	98

[a] See eq 1. Standard conditions: To a solution of $Ni(cod)_2$ (20 mol%), IPr (40 mol%) in THF at –78 °C were added the allene (100 mol%, 0.5 mmol), aldehyde (300 mol%), and silane (300 mol%). The mixture was warmed to ambient room temperature over 6 h, stirred 12 h, and purified by chromatography (SiO_2). Absolute configuration determined by Mosher ester analysis. See Supporting Information. [b] Ratio of allylic to the sum of all homoallylic products. [c] Determined by ^1H NMR of unpurified reaction mixtures. [d] Isolated yield of allylic alcohol shown. [e] Determined by chiral HPLC. [f] ^1H NMR of crude reaction mixture indicated a 94:6 ratio of **6f**:**6a** (reductive dechlorination).

A methyl group para to the carbonyl of the aldehyde had little effect on both the allylic:homoallylic selectivity and the *Z*/*E* selectivity (Table 6, entries 1 and 3), whereas an ortho methyl substituent resulted in slightly diminished reaction yield (70%) and slight increased in the amount of homoallylic products formed (90:10, entry 2).

The nickel-catalyzed allene–aldehyde coupling is compatible with ethers, esters, and aryl chlorides (Table 6, entries 4-6). An electron-donating MeO group in the para position had little effect on the transformation (entry 4), but an electron-withdrawing CO_2Me substituent reduced the chemical yield to 56% and the allylic:homoallylic selectivity to 90:10 (entry 5). In the case of a para Cl substituent (entry 6), a small amount of **6a**, corresponding to reductive dechlorination of **6f**, could be detected by ^{1}H NMR analysis of the crude reaction mixture (**6f**:**6a** = 94:6), but this impurity was easily removed by SiO_2 chromatography.

We next examined coupling reactions of enantiomerically enriched 1,3-allenes in which the two allene substituents were different, adding yet another selectivity variable in these reactions, site selectivity. In other words, two different allylic products are possible, depending upon which double bond of the allene reacts (Table 6, entries 7-10).

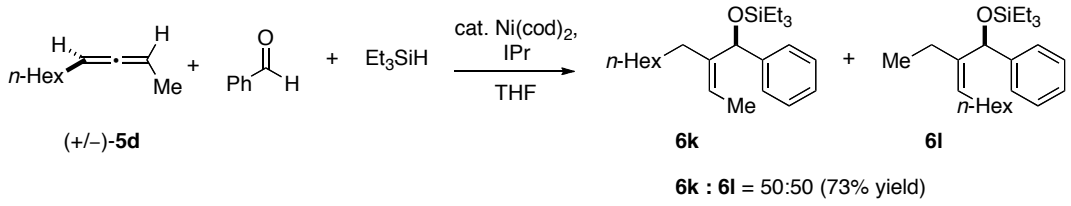
(a*S*)-1-Cyclohexyl-1,2-butadiene (**5b**, 98% ee), prepared using a similar sequence to that for (a*S*)-4,5-nonadiene (**5a**), underwent multicomponent coupling in 76% yield with benzaldehyde under the catalytic reaction conditions used in the previous examples (Table 6, entry 7). The ratio of allylic to homoallylic products was similarly high (93:7), as were both the *Z*/*E* selectivity and the enantiomeric purity of the product (**6g**, 98% ee). On the issue of site selectivity, a single allylic product was isolated, corresponding to exclusive reaction of the more hindered double bond of the allene.

These trends and high selectivity were preserved in analogous coupling reactions employing different organosilanes (Table 6, entries 8-9). The reactions leading to allylic products **6h** and **6i** proceeded with excellent allylic:homoallylic selectivity, in good yield, and with high enantio-, *Z*/*E*-, and site selectivity. These results also demonstrate a degree of flexibility as to which silyl "protective group" is incorporated into the product.

The coupling of (a*S*)-1-*tert*-butyl-1,2-butadiene (**5c**), benzaldehyde, and Et_3SiH afforded **6j** in reduced yield and allylic:homoallylic selectivity, but with the same level of *Z*/*E*-, enantio-, and site selectivity as that observed in all other cases (Table 6, entry 10).

The nickel/IPr catalyst system can differentiate the two alkyl groups on the allene only when the two alkyl groups have significant steric difference. As discussed in the case of allenes **5b** and **5c**, both allenes coupled with benzaldehyde with high site selectivity (i.e., only one allylic ether product was observed). This demonstrated that the nickel/IPr system could differentiate between a branched alkyl group and a methyl group. On the other hand, there was no differentiation between unbranched alkyl group and a methyl group. For example, the coupling of racemic *n*-hexyl-buta-1,2-diene (**5d**, Scheme 6) with benzaldehyde and triethylsilane yielded a 50:50 mixture of allylic ether products (**6k** and **6l**).

Scheme 6

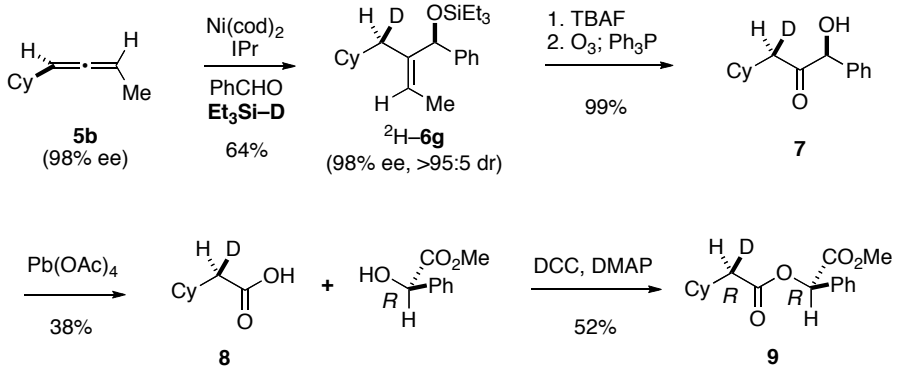


Deuterium Labeling Experiment

A deuterium labeling experiment was carried out to confirm the role of triethylsilane as a reducing agent. A previous experiment was repeated (Table 6, entry 7), using Et_3SiD (97% D) in place of Et_3SiH (Scheme 7). Slightly lower allylic:homoallylic selectivity (89:11) was observed, but ^{2}H-**6g** had the same ee, *Z*/*E* ratio, and site selectivity as **6g**. Moreover, deuterium incorporation occurred at a single site and with >95:5 diastereoselectivity. This confirmed the hydride on triethylsilane was incorporated into the coupling product.

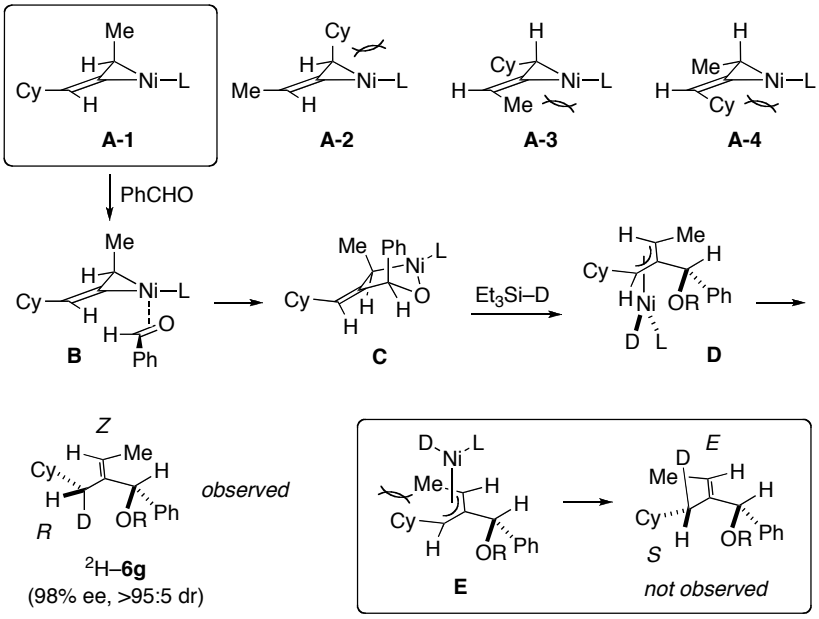
The configuration of the deuterium labeled stereogenic center was assigned as *R* by the sequence shown in Scheme 7. The triethylsilyl group of labeled coupling product ^{2}H-**6g** was removed with tetrabutylammonium fluoride, and ozonolysis of the double bond afforded hydroxyketone **7** in near quantitative yield. Lead tetraacetate cleavage of this functional group pair provided 2-deuterio-2-cyclohexylacetic acid (**8**). Esterification of **8** with methyl (*R*)-mandelate (DCC, DMAP) yielded **9**. Comparison of the ^{1}H NMR spectra of this compound to those of (+/–)-**9** and the corresponding unlabeled ester allowed for assignment of the labeled stereogenic center as the *R* configuration.[20]

Scheme 7



The general observation of the nickel-catalyzed allene–aldehyde coupling (Tables 4 and 6) and the result of the deuterium labeling experiment (Scheme 7) can be accounted for by the sequence of events proposed in Scheme 8. Of the four isomeric 1:1:1 complexes of Ni, IPr (L), and allene **5b** (**A-1**, **A-2**, **A-3**, and **A-4**), only **A-1** places the large Ni-L complex on the less hindered allene face *and* less substituted double bond. The sense of induction may be explained by benzaldehyde coordination away from the methyl group with the Ph group placed between L and (cyclohexyl)methylidene (**B**). Oxidative cyclization gives metallacycle **C**.

Scheme 8



We believe that there is a direct link between the selectivity for the *Z* alkene geometry and the sense of induction of deuterium labeling. Sigma bond metathesis between **C** and Et_3SiD could afford η^3-allyl-Ni complex **D**. Reductive elimination with retention leads to the observed *Z* alkene and *R* configuration at the labeled carbon. Conversely, the alternative complex (**E**) gives the opposite sense of selectivity in *both* cases (*E* and *S*, respectively). Our explanation for the absence of this product is the severe 1,3-interaction between the Me and Cy groups present in **E**.

Finally, the overall site selectivity (reduction of the more hindered double bond of the allene) could be explained by the reductive elimination step between the hydride and the allyl group on nickel. If nickel complex **D** was trigonal planar, either the small hydride or the large ligand on nickel would be underneath the cyclohexyl group on the allyl group. Based on a steric argument the hydride rather than the ligand would be next to the cyclohexyl group. Therefore reductive elimination placed the hydride to the allyl carbon with the cyclohexyl group to afford **6g**.

This proposed mechanism is also consistent with the result observed in the nickel-catalyzed coupling of terminal allenes and aldehydes. The more hindered double bond was reduced to provide germinal disubstituted allylic ether products (Table 4).

Conclusion

In summary, this enantioselective, three-component coupling occurs by way of a previously unobserved process in allene–aldehyde coupling reactions and is promoted by a Ni-NHC complex that efficiently transfers the axial chirality of the allene to the product. This catalyst also possesses the qualities necessary to induce a surprising sense and degree of *Z*/*E*- and site selectivity.

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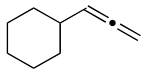
Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled over calcium hydride. Triethylsilane, triisopropylsilane and *tert*-butyldimethylsilane were purchased from Aldrich Chemical Co. and were saturated with nitrogen before use. Benzaldehyde was purchased from Aldrich Chemical Co. and was distilled before use. All aliphatic aldehydes were distilled over magnesium sulfate under argon before use. Bis(cyclooctadienyl)nickel(0) ($Ni(cod)_2$) and tricyclopentylphosphine (Cyp_3P) were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere and used without further purification. 1,3-Bis-(2,6-di-isopropylphenyl)imidazol-2-ylidene (IPr) was prepared according to literature procedure.[1] All other chemicals were used without purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometer in $CDCl_3$, unless otherwise noted. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns. Specific Rotations ($[\alpha]^{20}_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

Preparation of Terminal Allenes

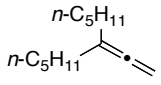


1a

Prepared by the method of Brandsma.[2] Cyclohexyl-magnesium chloride (50 mL, 100 mmol, 2 M in ether) was dissolved in anhydrous THF (80 mL) and cooled to –78 °C under argon. After 10 minutes of cooling, a THF (8 ml) solution of anhydrous lithium bromide (2 g) and anhydrous

copper (I) bromide (1 g) was added to the Grignard solution in one portion. The reaction mixture was stirred 20 min at –78 °C. Propargyl bromide (13.4 mL, 120 mmol) was dissolved in anhydrous THF (10 mL) in an oven dried round bottom flask and was cooled at –78 °C for 15 min. The propargyl bromide solution was taken up by a 50 mL syringe and added to the reaction mixture over 30 min. During this time the reaction mixture was kept below –50 °C with rigorous stirring. After the addition was complete the reaction mixture was stirred 30 min at –78 °C. The dry ice / acetone bath was removed and the reaction was allowed to warm to room temperature and stirred 3 h. The reaction mixture was poured into an aqueous NH_4Cl solution (10 g NH_4Cl, 100 mL). The mixture was extracted with 200 mL pentane. The aqueous layer was extracted again with 100 mL pentane. The combined pentane solution was washed repeatedly with water and finally with brine. The solution was dried with $MgSO_4$ and pentane was removed in rotavap. Purification via flash chromatography on silica followed by distillation afforded **1a** (7.9 g, 65% yield).

^{1}H NMR (500MHz, $CDCl_3$, δ): 5.10 (q, *J* = 6.4 Hz, 1H), 4.69 (dd, *J* = 6.7, 3.4 Hz, 2H), 1.99 (m, 1H), 1.80-1.02 (m, 11H).
^{13}C NMR (125MHz, $CDCl_3$, δ): 207.6, 96.3, 75.6, 36.8, 33.2, 26.4, 26.2.
IR (NaCl, thin film): 2925, 2852, 2662, 1955, 1445, 839.

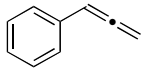


1b

2-octyn-1-ol (4.3 mL, 30 mmol) and triethylamine (17 mL, 120 mmol) were dissolved in anhydrous dichloromethane (35 mL) in a 100 mL round bottom flask. The reaction mixture was stirred 10 min at –78 °C. Methanesulfonyl choride (7 mL, 90 mmol) was added dropwise. After the addition was complete the reaction was stirred 2 h at –78 °C. The dry ice / acetone bath was replaced by a sodium chloride / ice slush bath. The reaction mixture was stirred 90 min at –10 °C. The reaction mixture was poured into water (50 mL). The organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined dichloromethane solution was washed with water and dried with $MgSO_4$. Purification via flash chromatography on silica afforded methanesulfonic acid oct-2-ynyl ester. In an oven dried 50 mL round bottom flask magnesium turning (0.56 g) was stirred in anhydrous THF (4 mL). A few drop of 1,2-dibromoethane was added. Gentle heating was applied to initiate the reaction. *n*-Pentylbromide (2.84 mL, 23 mmol) was added slowly at a rate that caused and maintained a gentle reflux. When most of the magnesium vanished of more *n*-pentylbromide (1 mL) was added. The solution was cooled down to slightly warm (pentylmagnesium bromide was not soluble in cold THF). Meanwhile anhydrous CuBr (3.44 g, 24 mmol) and anhydrous LiBr (2.08 g, 24 mmol) were dissolved in anhydrous THF (40 mL) in an ice bath and stirred vigorously. Once the mixture became homogeneous, the warm pentyl magnesium bromide solution was added via a syringe with a thick needle. The reaction mixture was stirred rigorously for 20 min at 0 °C. The reaction mixture was cooled to –78 °C. Methanesulfonic acid oct-2-ynyl ester in anhydrous THF (30 mL) was added to the reaction mixture dropwise via a syringe pump over 30 min. Once the addition was complete, the dry ice / acetone bath was allowed to warm back to room temperature and stirred 12 h. The reaction mixture was quenched with ice cold saturated NH_4Cl (80 mL) and extracted with 250 mL hexane. The aqueous layer was extracted again with hexane until the aqueous layer became blue. The combined hexane solution was then washed two times with

saturated NH_4Cl, once with water (50 mL) and finally with brine (50 mL). Purification via flash column chromatography on silica afforded allene **1b** (2.54 g, 47% from 2-octyn-1-ol).

^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.64 (p, *J* = 3.0 Hz, 2H), 1.96-1.90 (m, 4H), 1.46-1.39 (m, 4H), 1.35-1.26 (m, 8H), 0.94-0.87 (t, *J* = 7.0 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 205.9, 103.6, 75.4, 32.3, 31.8, 27.5, 22.8, 14.3.
IR (thin film NaCl): 2957, 2929, 2873, 2859, 1958, 843.



1c

Prepared according to the method of Myers.[3] Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH / ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred 10 min below –10 ºC. 1-Phenyl-2-propyn-1-ol (1.22 mL, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred 10 min, and *o*-nitrobenzenesulfonyl-hydrazine[3b] (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 ºC for 2 h and was allowed to warm to room temperature and stirred 16 h. The reaction was diluted with pentane (300 mL) and washed 5 times with ice cold water to remove THF. The mixture was dried by $MgSO_4$. Column chromatography in pentane afforded **1c** as a colorless oil (250 mg, 21% yield).

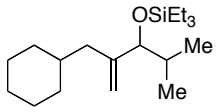
^{1}H NMR (400MHz, $CDCl_3$, δ): 7.40-7.28 (m, 4H), 7.25-7.16 (m, 1H), 6.18 (t, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 2H).

Nickel-Catalyzed Couplings of Terminal Allenes and Aldehydes

Standard procedure A. A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (28 mg, 0.1 mmol, 10 mol%) and Cyp_3P (28 μL, 0.1 mmol, 10 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (2 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (3 mmol, 300 mol%) was added in one portion. Aldehyde (3 mmol, 300 mol%) was added in one portion. Finally allene (1 mmol, 100 mol%) in THF (8 mL) was added into the reaction mixture at room temperature via a syringe pump over 8 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.

Standard procedure B. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (7 mg, 0.025 mmol, 10 mol%) and Cyp_3P (7 μL, 0.025 mmol, 10 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF or toluene (0.5 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (0.75 mmol, 300 mol%) was added in one portion. Aldehyde (0.75 mmol, 300 mol%) was added in one portion. Finally allene (0.25 mmol, 100 mol%) in THF or toluene (2 mL) was added into the reaction mixture at room temperature via a syringe pump over 3.5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.

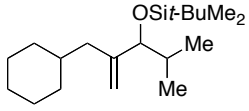
Standard procedure C. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (10 mg, 0.036 mmol, 15 mol%) and Cyp_3P (10 μL, 0.036 mmol, 15 mol%) were added to the flask. The flask was sealed with a septum and electrical tape. The sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (0.5 mL) at room temperature under argon and stirred 10 min at room temperature. Silane (0.75 mmol, 300 mol%) was added in one portion. Aldehyde (0.75 mmol, 300 mol%) was added in one portion. Finally allene (0.25 mmol, 100 mol%) in THF or toluene (3 mL) was added into the reaction mixture at room temperature via a syringe pump over 5 h. The reaction was stirred at room temperature for another 12 h. THF and other volatiles were removed under reduced pressure. The crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether product.



3b

The reaction of allene **1a** (148 μL, 1 mmol) and isobutyraldehyde (272 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and triethylsilane (480 μL, 3 mmol) in THF following the standard procedure A described above afforded **3b** in 52% yield.

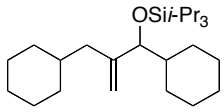
^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.72 (d, *J* = 6.1 Hz, 1H), 2.00-1.00 (m, 14 H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.85 (t, *J* = 6.32 Hz, 6H), 0.59 (q, *J* = 7.98 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 149.0, 111.0, 82.0, 39.4, 35.9, 34.1, 33.7, 31.8, 26.9, 26.7, 26.6, 20.1, 17.6, 7.3, 5.2.
IR (NaCl, thin film): 3077, 2955, 2923, 2877, 2853, 1811, 1646, 1459, 1449, 1414, 1063, 1007, 904, 834, 740, 725.
HRMS-ESI (*m* / *z*): $[M+Na]^+$ calcd for $C_{19}H_{38}OSiNa$, 333.2584; found, 333.2593.



3c

The reaction of allene **1a** (148 μL, 1 mmol) and isobutyraldehyde (272 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A described above afforded **3c** in 71% yield.

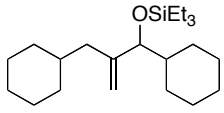
^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.98 (m, 1H), 4.80 (m, 1H), 3.70 (d, *J* = 5.8 Hz, 1H), 1.98-1.60 (m, 9H), 1.58-1.40 (m, 1H), 1.38-1.10 (m, 4H), 0.92 (s, 9H), 0.843 (dd, *J* = 6.9, 6.6, 6H), 0.04 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.8, 111.1, 81.5, 39.7, 35.7, 34.2, 33.6, 31.7, 26.9, 26.7, 26.6, 26.2, 20.3, 18.5, 17.3, -4.1, -4.8.
IR (NaCl, thin film): 3077, 2957, 2927, 2855, 1647, 1463, 1251, 1057, 863, 838, 774.
HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{38}OSiNa$, 333.2584; found, 333.2590.



3d

The reaction of allene **1a** (37 μL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and triisopropylsilane (154 μL, 0.75 mmol) in toluene following the standard procedure B described above (except that 1 mL toluene was used to dissolve $Ni(cod)_2$ and tricyclopentylphosphine and the reaction was heated at 50 ˚C) afforded **3d** in 24% yield.

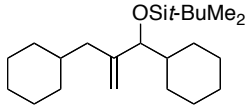
^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.96 (m, 1H), 4.82 (m, 1H), 3.95 (d, *J* = 5.8 Hz, 1H), 2.00-0.80 (m, 25H), 1.10 (s, 18H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.6, 110.9, 81.9, 42.8, 39.5, 35.6, 34.2, 33.8, 30.2, 28.6, 26.9, 26.8, 26.8, 26.7, 26.6, 18.5, 13.1.
IR (NaCl, thin film): 3079, 2924, 2865, 2852, 1645.71, 1449, 1086, 1062, 883.
HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{48}OSiNa$, 415.3367; found, 415.3366.



3e

The reaction of allene **1a** (148 μL, 1 mmol) and cyclohexanecarboxaldehyde (361 μL, 3 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and triethylsilane (480 μL, 3 mmol) in THF following the standard procedure A described above afforded **3e** in 46% yield.

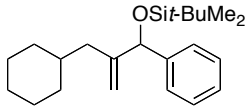
^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.93 (m, 1H), 4.79 (m, 1H), 3.72 (d, *J* = 6.7, 1H), 2.00-0.80 (m, 24H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.59 (q, 7.9 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.6, 111.1, 81.8, 41.5, 39.0, 35.6, 34.1, 33.7, 30.4, 28.4, 26.9, 26.9, 26.7, 26.7, 26.6, 26.5, 7.3, 5.2.
IR (NaCl, thin film): 3076, 2923, 2876, 2852, 1809, 1644, 1449, 1239, 1063, 1008, 898, 827, 740.
HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{42}OSiNa$, 373.2897; found, 373.2892.



3f

The reaction of allene **1a** (148 μL, 1 mmol) and cyclohexanecarboxaldehyde (361 μL, 3 mmol) with Ni(cod)$_2$, tricyclopentylphosphine and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A described above afforded **3f** in 73% yield.

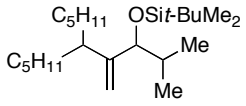
^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.94 (m, 1H), 4.80 (m, 1H), 3.70 (d, J = 6.1 Hz, 1H), 2.00-0.80 (m, 24H), 0.91 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 148.4, 111.2, 81.4, 41.5, 39.3, 35.6, 34.2, 33.7, 30.7, 28.1, 26.9, 26.9, 26.7, 26.7, 26.6, 26.6, 26.2, 18.5, -4.1, -4.7.
IR (NaCl, thin film): 3076, 2926, 1645, 1450, 1251, 1061, 900, 837, 774.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{42}OSiNa$, 373.2897; found, 373.2893.



3g

A 7 mL vial and a stir bar were oven-dried and brought into a glove box. Ni(cod)$_2$ (7 mg, 0.025 mmol, 10 mol%) and IPr (19 mg, 0.05 mmol, 20 mol%) were added to the flask. The vial was sealed with a septum and electrical tape. The sealed vial was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (3 mL) at room temperature under argon and stirred 10 min at room temperature. The mixture was cooled to –78 °C. *t*-BuMe$_2$SiH (125 μL, 0.75 mmol, 300 mol%) was added in one portion. Benzaldehyde (76 μL, 0.75 mmol, 300 mol%) was added in one portion. Finally allene (37 μL, 0.25 mmol, 100 mol%) was. The reaction was stirred 2 h at –78 °C. The dry ice / acetone bath was then covered with aluminum foil and the temperature was slowly rise to room temperature. The reaction was stirred for a total of 15 h. THF and other volatiles were removed under reduced pressure. Purification via flash chromatography on silica afforded **3g** in 86% yield.

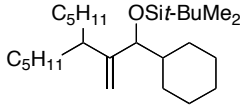
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.35-7.20 (m, 5H), 5.24 (s, 1H), 5.10 (s, 1H), 4.83 (s, 1H), 1.80 (m, 1H), 1.70 (m, 6H), 1.45 (m, 1H), 1.15 (m, 3H), 0.92 (s, 9H), 0.75 (m, 2H), 0.07 (s, 3H), -0.04 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.0, 143.7, 128.1, 127.1, 126.7, 110.9, 78.4, 39.5, 35.8, 33.7, 33.480, 26,8, 26.6, 26.5, 26.1, 18.5, -4.7, -4.7.
IR (NaCl, thin film): 2926, 2854, 1472, 1449, 1252, 1090, 1065, 867, 835, 776, 699.
HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{38}OSiNa$, 367.2428; found, 367.2431.



3h

The reaction of allene **1b** (57 μL, 0.25 mmol) and isobutyraldehyde (68 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure C described above afforded **3h** in 75% yield.

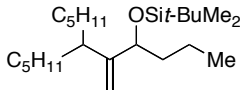
^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.10 (m, 1H), 4.83 (m, 1H), 3.79 (bs, 1H), 1.80-1.68 (m, 2H), 1.46-1.18 (m, 22H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 9H), 0.93-0.85 (m, 6H), 0.76 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.7, 108.3, 79.7, 41.4, 36.2, 34.0, 32.5, 32.5, 30.9, 27.5, 26.7, 26.2, 22.9, 22.9, 21.4, 18.5, 14.9, 14.4, 14.3, -3.9, -4.8.
IR (NaCl, thin film): 2958, 2929, 2858, 1647, 1463, 1250, 1056, 902, 865, 839, 774.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{48}OSiNa$, 391.3367; found, 391.3365.



3i

The reaction of allene **1b** (57 μL, 0.25 mmol) and cyclohexanecarboxaldehyde (90 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure B described above afforded **3i** in 68%.

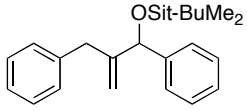
^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.06 (m, 1H), 4.83 (m, 1H), 3.76 (bs, 1H), 1.90-1.00 (m, 28H), 0.94 (s, 9H), 0.90 (m, 6H), 0.03 (s, 3H), 0.03 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.2, 108.4, 79.8, 41.2, 41.1, 36.2, 34.2, 32.5, 32.5, 32.1, 27.4, 27.1, 27.0, 26.8, 26.6, 26.3, 25.5, 22.9, 22.925, 18.5, 14.4, 14.3, -3.9, -4.7.
IR (NaCl, thin film): 2929, 2856, 1647, 1463, 1251, 1103, 902, 835, 774.
HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{26}H_{52}OSiNa$, 431.3680; found, 431.3700.



3j

The reaction of allene **1b** (57 μL, 0.25 mmol) and *n*-butyraldehyde (68 μL, 0.75 mmol) with $Ni(cod)_2$, tricyclopentylphosphine and *tert*-butyldimethylsilane (125 μL, 0.75 mmol) in THF following the standard procedure C described above afforded **3j** in 35% yield.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.09 (bs, 1H), 4.76 (bs, 1H), 3.97 (t, *J* = 4.9 Hz, 1H), 1.90-1.82 (m, 1H), 1.55-1.20 (m, 23H), 0.92 (s, 9H), 0.88 (m, 6H), 0.05 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 156.0, 107.6, 75.8, 40.7, 39.1, 35.9, 34.7, 32.5, 27.4, 26.9, 26.2, 22.9, 18.8, 18.5, 14.4, 14.3, -4.2, -4.7.
IR (NaCl, thin film): 2958, 2930, 2858, 1646, 1463, 1255, 1085, 902, 836, 774.
HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{23}H_{48}OSiNa$, 391.3367; found, 391.3350.

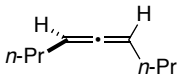


3k

The reaction of phenylallene **1c** (121 μL, 1 mmol) and benzaldehyde (305 μL, 3 mmol) with $Ni(cod)_2$, IPr (78 mg, 0.2 mmol) and *tert*-butyldimethylsilane (498 μL, 3 mmol) in THF following the standard procedure A (described above except that tricyclopentylphosphine was replaced by IPr) afforded **3k** in 56% yield.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43-7.33 (m, 4H), 7.30 (t, *J* = 7.4 Hz, 3H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.0, 2H), 5.35 (s, 1H), 5.19 (s, 1H), 4.71 (d, *J* = 1.4 Hz, 1H), 3.39 (d, *J* = 16.1 Hz, 1H), 3.05 (d, *J* = 16.1 Hz, 1H), 0.97 (s, 9H), 0.09 (s, 3H), -0.02 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 151.8, 143.3, 139.7, 129.6, 128.4, 128.2, 127.3, 126.6, 126.1, 112.1, 77.8, 37.6, 26.1, 18.5, -4.7, -4.8.
IR (NaCl, thin film): 3028, 2956, 2929, 2857, 1648, 1602, 1494, 1251, 1091, 1067, 868, 835, 776, 699.
HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{30}OSiNa$, 361.1958; found, 361.1959.

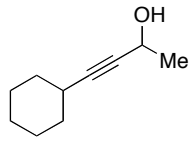
Preparation of chiral allenes



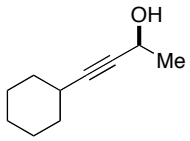
(a*S*)-**5a**

Prepared using the same method as **5b** and **5c** from (*S*)-non-5-yn-4-ol, which was prepared by lipase resolution using the procedure described below (60% yield from (*S*)-non-5-yn-4-ol, 95% ee by chiral GC). The absolute configuration was assigned by comparing the specific rotation of **5a** with the literature value[4] and is also consistent with the Lowes-Brewster rule.[5]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.07 (m, 2H), 1.97 (m, 4H), 1.44 (sextet, J = 7.3 Hz, 4H), 0.94 (t, J = 7.3 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 204.2, 90.8, 31.4, 22.7, 13.9.
IR (NaCl, thin film): 2960, 2931, 1963, 1464, 879.
$[\alpha]^{20}_D$ +64.0 (*c* 1.00, $CHCl_3$)
$[\alpha]^{20}_D$ +84.7 (*c* 0.72, EtOH)
Literature $[\alpha]^{20}_D$ +80.0 (*c* 0.69, EtOH)[4]
Chiral GC analysis: (Chiraldex B-PH, 35 ºC isotherm, 0.1 mL/min): t_R(a*R*) = 74.7 min; t_R(a*S*) = 81.2 min.



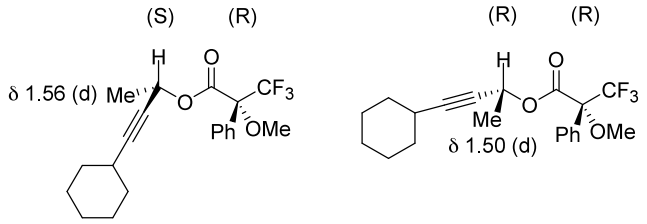
Preparation of (+/–)-4-cyclohexyl-but-3-yn-2-ol. Carbon-tetrabromide (73 g, 220 mmol) was dissolved in anhydrous dichloromethane (150 mL). The solution was cooled to 0 ºC, triphenylphosphine (115 g, 440 mmol) was added. The mixture was stirred 30 min at 0 ºC. Cyclohexanecarboxaldehyde (10 mL, 110 mmol) was added and the reaction mixture was slowly warmed to room temperature and stirred 12 h. The brown precipitate was removed by filtering the CH_2Cl_2 solution through silica gel and the silica gel was washed with hexane. Evaporation of the solvents gave an oil with white precipitate. The crude was diluted with hexane and filtered through silica gel to yield a colorless oil (2,2-dibromo-vinyl)-cyclohexane (21.62 g, 74% yield). It was used without further purification. (2,2-Dibromo-vinyl)-cyclohexane (9.18 g, 34 mmol) was dissolved in anhydrous THF (40 mL) and was cooled to –78 ºC. Methyllithium (55 mL, 88 mmol, 1.6 M in ether) was added to the solution over 5 min and the mixture was stirred 2.5 h at –78 ºC. Acetaldehyde was added in one portion and the mixture was stirred 1.5 h and was warmed to room temperature. The reaction was quenched with water and extracted with diethylether (80 mL), which was washed with water and dried with $MgSO_4$. Column chromatography afforded a yellow oil of (+/–)-4-cyclohexyl-but-3-yn-2-ol (4.9 g, 94% yield).



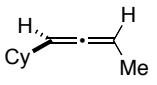
Preparation of enantiomerically enriched (*S*)-4-cyclohexyl-but-3-yn-2-ol by lipase resolution.[6] In an oven-dried round bottom flask, (+/–)- 4-cyclohexyl-but-3-yn-2-ol (2.28 g, 15 mmol) was dissolved in anhydrous pentane (50 mL) at room temperature. 4Å molecular sieves (approximately half the volume of the solvent), Amano lipase AK from *Pseudomonas fluorescens* (2 g) followed by freshly distilled vinyl acetate (4 mL, 40 mmol) were added. The slurry was stirred 5 h at room temperature. NMR of the crude reaction mixture indicated that the ratio of acetate to alcohol was approximately 1:1. The mixture was stirred for 30 more minutes, filtered through celite and washed with pentane. Column chromatography afforded (*S*)-4-cyclo-hexyl-but-3-yn-2-ol (1.1 g, 99% yield based on 50% conversion) that was at least 98% ee according to Mosher's ester analysis. The absolute configuration was determined by Mosher's ester analysis.[7] It was consistent with the specific rotations of similar compounds prepared from the same method.[6]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.53 (m, 1H), 2.42-2.30 (m, 1H), 1.9-1.2 (m, 10H), 1.43 (d, J = 6.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 89.0, 82.3, 58.8, 32.8, 29.1, 26.0, 25.1.
IR (NaCl, thin film): 3333, 2931, 2854, 2240, 1449, 1158, 1078, 897.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{16}ONa$, 175.1093; found, 175.1094.
$[\alpha]^{20}_D$ –23.0 (*c* 1.00, $CHCl_3$)

Mosher's ester analysis: (+/–)-4-cyclohexyl-but-3-yn-2-ol was converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2). The methyl doublets (δ 1.50 and 1.56 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[7]



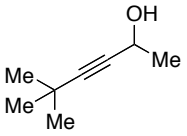
The enantiomerically-enriched alcohol was then converted to (*R*)-Mosher's ester, and a doublet was observed at δ 1.56 ppm. Therefore, 4-cyclo-hexyl-but-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (*S*).



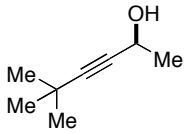
(a*S*)-**5b**

Prepared using the method of Myers.[3] Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH / ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred 10 min below –10 ºC. (*S*)-4-cyclohexyl-but-3-yn-2-ol (1.52 g, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred 10 min, and *o*-nitrobenzenesulfonyl-hydrazine (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 ºC for 2 h and was allowed to warm to room temperature and stirred 16 h. The reaction was cooled to 0 ºC, diluted with pentane (200 mL) and washed 10 times with ice cold water to remove THF. Column chromatography in pentane afforded **5b** (0.95 g, 70% yield, 98% ee based on chiral GC analysis). The absolute configuration of the allene was determined based on the absolute configuration of the alcohol and was consistent with Lowes-Brewster rule.[5] The spectral data are consistent with literature values.[8]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.09 (m, 1H), 5.04 (m, 1H), 2.00-1.91 (m, 1H), 1.80-1.00 (m, 10H), 1.65 (dd, J = 3.4, 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 203.7, 96.7, 86.5, 37.4, 33.3, 26.4, 26.3, 15.0.
IR (NaCl, thin film): 2924, 2852, 1965, 1448, 960, 869, 711.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{16}Na$, 136.1247; found, 136.1249.
$[\alpha]^{20}_D$ + 76.7 (*c* 1.46, $CHCl_3$)
Chiral GC analysis: (Chiraldex B-DA, 60 ºC isotherm, 1.5 mL/min): t_R(a*S*) = 21.1 min; t_R(a*R*) = 22.6 min.



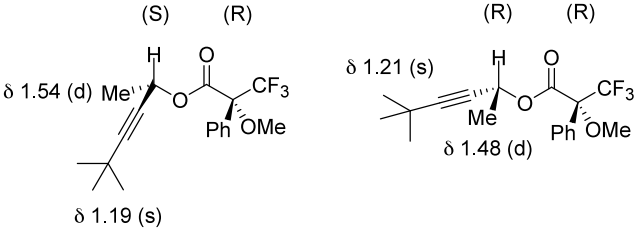
Preparation of (+/–)-5,5-dimethyl-hex-3-yn-2-ol. THF (80 mL) was cooled to –78 ºC. *tert*-butylacetylene (7.35 mL, 60 mmol) was added. MeLi (56 mL, 90 mmol, 1.6 M in diethylether) was added via a syringe pump over 10 min. The mixture was stirred 1 h at –78 ºC. Acetaldehyde (6.7 mL, 120 mmol) was added. The mixture was stirred at –78 ºC for one more hour and warmed to room temperature. The reaction was cooled to 0 ºC and quenched with water. The cold mixture was diluted with diethylether (150 mL) and washed two times with water. The ether solution was dried by $MgSO_4$ and was filtered through silica gel. The silica gel was washed with diethyl ether. The NMR of the crude reaction mixture indicated 5,5-dimethyl-hex-3-yn-2-ol along with some cyclotrimer of acetaldehyde. (53.4 mmol alcohol based on NMR integration, 89% yield). The crude product was used without further purification.



Preparation of (*S*)-5,5-dimethyl-hex-3-yn-2-ol by lipase resolution. Prepared using the same lipase resolution procedure as described above (lipase, 4Å MS, vinylacetate, pentane, room temperature, 5.5 h. 88.5% isolated yield. > 98% ee based on chiral GC analysis and Mosher's ester analysis).

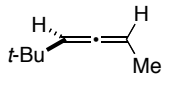
^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.49 (q, *J* = 6.5 Hz, 1H), 2.1 (bs, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 92.9, 80.9, 68.1, 58.6, 31.2, 25.0.
IR (NaCl, thin film): 3336, 2971, 2237, 1363, 1263, 1125, 1050, 973, 882.
$[\alpha]^{20}_D$ –27.3 (*c* 1.06, $CHCl_3$)

Mosher's ester analysis: (+/–)-5,5-dimethyl-hex-3-yn-2-ol was converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2). The methyl doublets (δ 1.48 and 1.54 ppm) and *t*-Bu singlets (δ 1.19 and 1.21 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[7]



The enantiomerically enriched alcohol was converted to (*R*)-Mosher's ester. A doublet was observed at δ 1.54 ppm, and a singlet was observed at δ 1.19 ppm. Therefore, 5,5-dimethyl-hex-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (*S*).

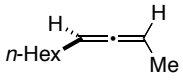
Chiral GC analysis: (Chiraldex B-PH, 60 ºC isotherm, 0.3 mL/min): t_R(*S*) = 69.0 min; t_R(*R*) = 72.3 min.



(a*S*)-**5c**

Prepared using the same method as described above for **5b**. After the removal of THF by an aqueous workup, the pentane solution was filtered through a pad of silica gel to remove most of the by-products. The pentane was removed by rotavap at atmospheric pressure, and the last traces of pentane were removed by fractional distillation. Finally, the product was separated from the crude mixture by distilling under high vacuum at room temperature, collecting in a cooled flask, affording 60% of **5c**. The absolute configuration of the allene was assigned based on the absolute configuration of the alcohol and was consistent with Lowes-Brewster rule.[5]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.12 (quintet , J = 6.8 Hz, 1H), 5.06 (dq, J = 3.3, 6.42 Hz, 1H), 1.67 (dd, J = 3.3, 6.9 Hz, 3H), 1.04 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 202.1, 102.6, 87.4, 31.9, 30.4, 15.1.
IR (NaCl, thin film): 2962, 1962, 1462, 1363, 1192, 873, 725.
$[\alpha]^{20}_D$ +67.7 (*c* 1.24, $CHCl_3$) (consistent with similar compounds)[9]



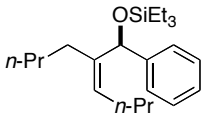
(+/–)-**5d**

Prepared using the same method as **5b** and **5c** from (+/–)-dec-3-yn-2-ol.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.04 (m, 2H), 1.96 (m, 2H), 1.65 (dd, J = 5.2, 10 Hz, 3H), 1.45-1.23 (m, 8H), 0.90 (t, J = 6.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 204.9, 90.5, 85.2, 31.9, 29.3, 29.1, 28.9, 22.9, 14.8, 14.3; IR (NaCl, thin film): 2963, 2928, 2857, 1967, 1460.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_{18}Na$, 138.1403; found, 138.1406.

Nickel-Catalyzed Reductive Coupling of Chiral Allenes and Aldehydes

General procedure. A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (28 mg, 0.1 mmol, 20 mol%) and IPr (78 mg, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (7.5 mL) under argon and stirred 10 min at room temperature. The solution was cooled to –78 ºC in a dry ice / acetone bath. After 10 min of cooling, triethylsilane (240 μL, 1.5 mmol, 300 mol%), *tert*-butyldimethylsilane (250 μL, 1.5 mmol, 300 mol%), or dimethylphenylsilane (233 μL, 1.5 mmol, 300 mol%), as specified below, was added in one portion. Next the aldehyde (1.5 mmol, 300 mol%) was added in one portion. The mixture was stirred 5 min at –78 ºC. The allene (0.5 mmol, 100 mol%) was added to the reaction mixture in one portion. The reaction was kept in the dry ice / acetone bath and the bath was allowed to warm to room temperature over 6 h. The reaction was stirred an additional 12 h at room temperature. ^{1}H NMR of an aliquot of the crude (after filtering through a plug of silica) indicated the allylic alcohol was the major coupling product along with minor impurities assigned as various homoallylic alcohols. The ratio of the allylic to homoallylic products was determined by the ^{1}H NMR integration of spectrum of the crude mixture (Refer to **Table 6** for the ratio). THF and excess silane were removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic ether coupling product.



6a

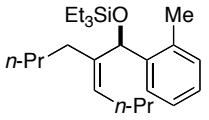
The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6a** in 77% isolated yield and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher's ester analysis to be *R*. The olefin geometry was determined to be Z by a nOe experiment (see below).

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.16-7.40 (m, 5H); 5.76 (s, 1H); 5.24 (t, *J* = 7.3 Hz, 1H); 2.27 (q, *J* = 7.5 Hz, 2H); 2.02 (m, 1H); 1.74 (m, 1H); 1.51 (sextet, *J* = 7.5 Hz, 2H); 1.14-1.34 (m, 4H); 1.01 (t, *J* = 6.7 Hz, 3H); 0.97 (t, *J* = 7.6 Hz, 9H); 0.81 (t, *J* = 7.0 Hz, 3H); 0.64 (q, *J* = 7.9 Hz).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.5, 141.9, 128.0, 126.5, 125.6, 125.4, 71.3, 31.0, 30.4, 29.6, 23.6, 22.9, 14.34, 14.26, 7.11, 7.07.
IR (NaCl, thin film): 2957, 2875, 1458, 1063, 742, 698.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{38}OSiNa$, 369.2584; found, 369.2588.
$[\alpha]^{20}_D$ –75.2 (*c* 1.07, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6a** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 9.7 min; $t_R(R)$ = 10.8 min.

Mosher's ester analysis:[7] (+/–)-**6a** was first converted into the free alcohol (TBAF, THF) and was then converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2). The vinyl triplets (δ 5.45 and 5.51 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher. The enantiomerically-enriched **6a** was then converted to (*R*)-Mosher's ester using the same procedure.[24] The vinyl triplet was observed at δ 5.46 ppm. Therefore **6a** had an absolute configuration of (*R*).

NOE DIFF experiment: Pre-saturation of the carbinol proton of **6a** gave no nOe to the vinylic proton (δ 5.24 ppm), but 13% nOe was observed for the allylic protons indicated (δ 2.27 ppm). These results supported a *Z* olefin geometry.

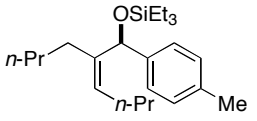


6b

The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and *o*-tolualdehyde (174 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6b** in 66% yield and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configurations were established by Mosher's ester analysis.[7]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.71 (bd, *J* = 7.6 Hz, 1H), 7.21 (bt, *J* = 7.4 Hz, 1H), 7.13 (dt, *J* = 1.4, 7.4 Hz, 1H), 7.04 (bd, *J* = 7.4 Hz, 1H), 5.75 (s, 1H), 5.20 (t, *J* = 6.6 Hz, 1H), 2.38-2.22 (dq, *J* = 7.5, 14.8 Hz, 2H), 2.20 (s, 3H), 1.91 (ddt, *J* = 1.1, 5.4, 10.32 Hz, 1H), 1.65 (ddt, *J* = 1.0, 6.7, 9.8 Hz, 1H), 1.49 (sextet, *J* = 6.9 Hz, 2H), 1.16 (m, 3H), 1.03 (t, *J* = 5.6 Hz, 4H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.77 (t, *J* = 7.1 Hz, 3H), 0.60 (q, *J* = 7.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.2, 139.1, 134.2, 129.8, 126.9, 126.7, 126.5, 125.6, 69.1, 31.7, 30.6, 30.5, 23.5, 22.8, 19.6, 14.4, 14.2, 7.1, 5.2.
IR (NaCl, thin film): 2957, 2875, 1462, 1061, 1006, 744.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{40}OSiNa$, 383.2741; found, 383.2737.
$[\alpha]^{20}_D$ –75.2 (*c* 1.25, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6b** (TBAF, THF) (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 11.4 min; $t_R(R)$ = 14.1 min.

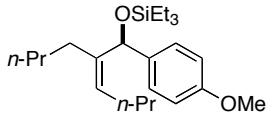


6c

The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and *p*-tolualdehyde (177 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6c** in 74% yield and 95% enantiomeric excess as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.24 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.74 (s, 1H), 5.22 (t, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 2.27 (q, *J* = 7.3 Hz, 2H), 2.03 (m, 1H), 1.74 (m, 1H), 1.50 (sextet, *J* = 7.3 Hz, 2H), 1.38-1.18 (m, 4H), 1.00 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.82 (t, *J* = 7.0 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.0, 141.5, 136.0, 128.7, 125.6, 125.1, 71.2, 31.0, 30.3, 29.6, 23.6, 22.9, 21.3, 14.33, 14.28, 7.1, 5.1.
IR (NaCl, thin film): 2957, 2875, 1458, 1073, 1006, 741.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{40}OSiNa$, 383.2741; found, 383.2747.
$[\alpha]^{20}_D$ –83.8 (*c* 1.05, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6c** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 100:0, 1.5 mL/min): $t_R(R)$ = 37.7 min; $t_R(S)$ = 49.1 min.

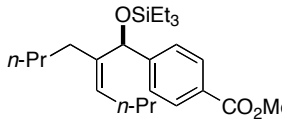


6d

The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and *p*-anisaldehyde (183 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6d** in 75% yield and 95% enantiomeric excess as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.28 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.73 (s, 1H), 5.23 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 2.26 (q, *J* = 7.6 Hz, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.50 (sextet, *J* = 7.2 Hz, 2H), 1.40-1.15 (m, 4H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.84 (t, *J* = 7.0, 3H), 0.64 (q, *J* = 7.6 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.3, 142.1, 136.7, 126.7, 125.1, 113.4, 71.0, 55.4, 31.0, 30.3, 29.6, 23.6, 22.9, 14.33, 14.28, 7.1, 5.1.
IR (NaCl, thin film): 2956, 2875, 1510, 1464, 1246, 1071, 741.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{40}O_2SiNa$, 399.2690; found, 399.2688.
$[\alpha]^{20}_D$ –67.5 (*c* 1.14, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6d** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(R)$ = 14.3 min; $t_R(S)$ = 17.0 min.



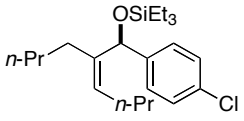
6e

The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and methyl 4-formylbenzoate (246 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6e** in 56% yield (co-eluted with a small amount of homoallylic alcohol minor products) and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.98 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.0, 2H), 5.79 (s, 1H), 5.26 (t, *J* = 7.0 Hz, 1H), 3.90 (s, 3H), 2.28 (q, *J* = 7.1 Hz, 2H), 1.95 (m, 1H), 1.72 (m, 1H), 1.55 (sextet, *J* = 7.0 Hz, 2H), 1.30-1.10 (m, 4H), 1.01 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 9H), 0.79 (t, *J* = 7.3 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.4, 150.1, 141.3, 129.4, 128.5, 126.1, 125.6, 71.2, 52.2, 31.0, 30.4, 29.6, 23.5, 22.8, 14.3, 14.2, 7.06, 5.01.
IR (NaCl, thin film): 2956, 1727, 1277, 1075, 1018, 743.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{24}H_{40}O_3SiNa$, 427.2639; found, 427.2658.
$[\alpha]^{20}_D$ –108.6 (*c* 1.28, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6e** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 95:5, 1.0 mL/min): $t_R(R)$ = 7.5 min; $t_R(S)$ = 19.7 min.

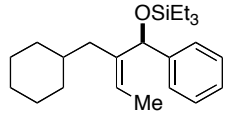


6f

The reaction of (a*S*)-nona-4,5-diene (**5a**) (82 μL, 0.5 mmol) and *p*-chlorobenzaldehyde solution (211 μL aldehyde, 1.5 mmol in 1 mL THF) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above yielded **6f** in 65% yield and 1% of dechlorinated product, ie, **6a** (total 66% isolated yield, ratio of **6f** : **6a** in crude NMR is 94:6) and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.4-7.2 (m, 4H), 5.73 (s, 1H), 5.26 (t, *J* = 7.0 Hz, 1H), 2.27 (q, J = 7.3 Hz, 2H), 2.00 (m, 1H), 1.72 (m, 1H), 1.51 (sextet, *J* = 7.4 Hz, 2H), 1.40-1.10 (m, 4H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.83 (t, *J* = 7.3 Hz, 3H), 0.64 (q, *J* = 8.0 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 143.2, 141.5, 132.2, 128.1, 127.1, 125.8, 70.9, 31.0, 30.4, 29.6, 23.6, 22.9, 14.3, 14.2, 7.1, 5.1.
IR (NaCl, thin film): 2957, 1488, 1074, 1014, 726.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{37}OClSiNa$, 403.2194; found, 403.2196.
$[\alpha]^{20}_D$ –88.9 (*c* 1.17, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6f** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 7.4 min; $t_R(R)$ = 8.6 min.



6g

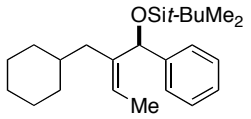
The reaction of **5b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6g** in 76% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by

Mosher's ester analysis. The olefin geometry was determined to be Z by a nOe experiment (see below).

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.79 (s, 1H), 5.30 (q, *J* = 7.0 Hz, 1H), 1.88 (d, *J* = 6.7 Hz, 3H), 1.80 (dd, *J* = 6.5, 14.5 Hz, 1H), 1.68 (dd, *J* = 7.0, 14.5 Hz), 1.64-1.54 (m, 6H), 1.28-1.18 (m, 1H), 1.12-1.00 (m, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.76-0.58 (m, 1H), 0.64 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 140.8, 128.0, 126.5, 125.6, 120.4, 70.9, 39.2, 36.1, 33.8, 33.5, 27.0, 26.7, 13.9, 7.1, 5.1.
IR (NaCl, thin film): 2954, 2921, 1449, 1091, 1064, 863, 737.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{38}OSiNa$, 381.2584; found, 381.2589.
$[\alpha]^{20}_D$ –58.0 (*c* 1.12, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6g** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 11.3 min; $t_R(R)$ = 17.4 min.

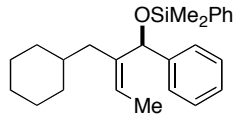
NOE DIFF experiment: Pre-saturation of the carbinol proton (δ 5.79 ppm) of **6g** gave no nOe to the vinylic proton (δ 5.30 ppm). A 10.7% nOe to the methyl group, however, was observed. Similarly, pre-saturation of the methyl protons (δ 1.88 ppm) did not show any nOe to the cyclohexyl protons. A 4.5% nOe to the carbinol proton (δ 5.79 ppm), however, was observed.



6h

The reaction of **5b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and *tert*-butyldimethyl-silane in THF following the general procedure described above afforded **6h** in 68% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40-7.10 (m, 5H), 5.80 (s, 1H), 5.31 (q, *J* = 7.0 Hz, 1H), 1.88 (d, *J* = 7.0 Hz, 3H), 1.77 (dd, *J* = 7.1, 14.8 Hz, 1H), 1.66 (dd, *J* = 7.0, 14.6 Hz, 1H), 1.57 (m, 6H), 1.30-0.50 (m, 5H), 0.96 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.5, 140.5, 127.9, 126.5, 125.6, 120.5, 71.1, 39.1, 35.9, 33.8, 33.5, 26.9, 26.6, 26.2, 18.6, 13.8, -4.6, -4.8.
IR (NaCl, thin film): 2926, 2854, 1449, 1252, 1090, 1064, 876, 835, 775, 698.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{38}OSiNa$, 381.2584; found, 381.2595
$[\alpha]^{20}_D$ –55.9 (*c* 1.11, $CHCl_3$)
Chiral HPLC analysis: Analysis was performed **6h** without the deprotection of the silane protected alcohol: (Chiralcel OD-H, hexanes: 2-propanol, 100:0, 0.8 mL/min): $t_R(R)$ = 4.1 min; $t_R(S)$ = 4.4 min.

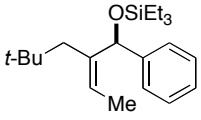


6i

The reaction of **5b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and dimethylphenylsilane in THF following the general procedure described above afforded **6i** in 65% isolated yield and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **6a** and **6j** whose configuration were established by Mosher's ester analysis.

^{1}H NMR (500 MHz, C_6D_6, δ): 7.66-7.61 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.24-7.18 (m, 5H), 7.09 (t, *J* = 7.3 Hz, 1H), 5.89 (s, 1H), 5.25 (q, *J* = 6.7 Hz, 1H), 2.02 (dd, *J* = 7.0, 14.7 Hz, 1H), 1.93 (dd, *J* = 7.0, 14.7 Hz, 1H), 1.74-1.58 (m, 5H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.35 (m, 1H), 1.10 (m, 3H), 0.82-0.60 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.0, 139.9, 138.2, 133.8, 129.7, 127.99, 127.96, 126.6, 125.6, 121.1, 71.4, 39.1, 36.1, 33.8, 33.5, 26.9, 26.6, 13.6, -0.9, -1.0.
IR (NaCl, thin film): 2921, 2850, 1449, 1428, 1251, 1118, 1088, 1057, 881, 829, 785, 737, 698.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{25}H_{34}OSiNa$, 401.2271; found, 401.2265.
$[\alpha]^{20}_D$ –19.0 (*c* 1.00, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6i** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 11.3 min; $t_R(R)$ = 17.4 min.



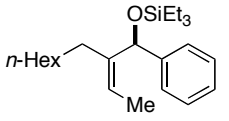
6j

The reaction of **5c** (55 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane in THF following the general procedure described above afforded **6j** in 40% isolated yield (co-eluted with a homoallylic alcohol minor product) and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher's ester analysis to be *R*.

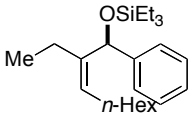
^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.72 (s, 1H), 5.46 (q, *J* = 7.0 Hz, 1H), 1.91 (d, *J* = 7.0 Hz, 3H), 1.86 (d, *J* = 14.6 Hz, 1H), 1.77 (d, *J* = 14.6 Hz, 1H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.80 (s, 9H), 0.61 (qd, *J* = 2.4, 7.6 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.7, 140.5, 127.8, 126.4, 125.9, 122.9, 71.7, 43.3, 30.7, 22.7, 14.0, 6.9, 4.9.
IR (NaCl, thin film): 2954, 1463, 1091, 1065, 1006, 742.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{36}OSiNa$, 355.2428; found, 355.2427.
$[\alpha]^{20}_D$ –29.8 (*c* 1.14, $CHCl_3$)

Chiral HPLC analysis: Analysis was performed on the corresponding free alcohol, obtained by the deprotection of **6j** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 10.4 min; $t_R(R)$ = 13.3 min.

Mosher's ester analysis: (+/–)-**6j** was first converted into the free alcohol (TBAF, THF) and then into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2). The vinylic quartets (δ 5.63 and 5.70 ppm) and the *t*-Bu singlets (δ 0.76 and 0.80 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[7] The enantiomerically enriched **6j** was then converted to (*R*)-Mosher's ester using the same procedure. The vinylic quartet was observed at δ 5.64 ppm, and the *t*-Bu singlet was observed at δ 0.75 ppm. Therefore, **3a** had an absolute configuration of (*R*).



6k and



6l

The reaction of **5d** (13.8 mg, 0.1 mmol) and benzaldehyde (32 μL, 0.3 mmol) with $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 20 mol%), IPr (16 mg, 0.04 mmol, 40 mol%) and triethylsilane (50 μL, 0.3 mmol, 300 mol%) in THF (1.5 ml) following general procedure described above afforded **6k** and **6l** in 1:1 ratio in 73% yield as determined by NMR versus an internal standard.

6k:

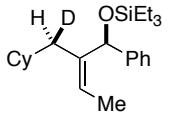
^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, *J* = 6.9 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.79 (s, 1H), 5.34 (q, *J* = 7.0 Hz, 1H), 1.99 (m, 1H), 1.86 (d, *J* = 7.0 Hz, 1H), 1.73 (m, 1H), 1.36-1.10 (m, 10 H), 0.97 (t, *J* = 8.2, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.63 (q, *J* = 7.6 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 143.1, 128.0, 126.5, 125.6, 118.9, 70.7, 32.1, 30.0, 29.8, 29.5, 28.7, 22.9, 14.4, 13.8, 7.1, 5.1.

6l

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.36 (d, *J* = 7.0 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.0 Hz, 1H), 5.78 (s, 1H), 5.23 (t, *J* = 7.0 Hz, 1H), 2.29 (m, 2H), 2.10 (sextet, *J* = 7.6 Hz, 1H), 1.73 (sextet, *J* = 7.6 Hz, 1H), 1.52-1.28 (m, 8 H), 0.96 (t, *J* = 8.2, 9H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.63 (q, *J* = 7.6 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 143.1, 128.0, 126.5, 125.7, 124.7, 71.3, 32.1, 30.5, 29.6, 28.3, 22.9, 22.3, 14.4, 12.8, 7.1, 5.1.

Deuterium Labeling Experiment

^{2}H-6g was converted to a mandelic acid ester **9** to determine the absolute configuration of the deuterated stereocenter using ^{1}H NMR by Parker's method.[10] The same mandelic acid derivative was also prepared by Fleming[11] and was also analyzed by the method of Parker.

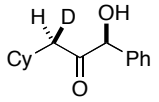


^{2}H-6g

The reaction of **5b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, IPr and triethylsilane-d (239 μL, 1.5 mmol) in THF, following the general procedure described above afforded ^{2}H-**6g** (111 mg, 64% yield) in 98% ee as determined by chiral HPLC and > 95:5 dr as determined by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.78 (s, 1H), 5.28 (q, *J* = 6.9 Hz, 1H), 1.87 (d, *J* = 7.0 Hz, 3H), 1.76 (bd, *J* = 6.6 Hz, 1H), 1.62-1.52 (m, 6H), 1.26-1.16 (m, 1H), 1.12-1.00 (m, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.76-0.58 (m, 1H), 0.62 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 140.7, 127.9, 126.5, 125.6, 120.4, 70.9, 38.8 (t, *J* = 19.5 Hz), 36.0, 33.8, 33.5, 26.9, 26.6, 13.9, 7.1, 5.1.
IR (NaCl, thin film): 2920, 1448, 1090, 1064, 731.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{37}DOSiNa$, 382.2647; found, 382.2643.
$[\alpha]^{20}_D$ –57.8 (*c* 1.02, $CHCl_3$)

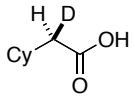
Chiral HPLC analysis: Analysis was performed on the deprotected ^{2}H-**6g** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$ = 11.1 min; $t_R(R)$ = 17.3 min.



7

^{2}H-**6g** (96 mg, 0.27 mmol) was stirred 30 min in TBAF (1 mL, 0.5 mmol, 0.5M in THF). The mixture was diluted in diethylether and washed with water. The ether solution was dried in $MgSO_4$, and the solvent was removed under reduced pressure. The crude was dissolved in CH_2Cl_2 (5 mL) and was cooled to –78 ºC. Ozone was bubbled through the solution for 20 min, and the solution turned blue. After purging with oxygen (2 min) triphenylphosphine (157 mg, 0.6 mmol in 5 mL CH_2Cl_2) was added in one portion at –78 ºC, stirred 5 min, and warmed to room temperature. CH_2Cl_2 was removed under reduced pressure. Column chromatography first with 20% CH_2Cl_2 / hexane removed triphenylphosphine. A gradient of 10-20 % EtOAc / Hexane afforded **7** (62 mg, 99% yield) in > 95:5 dr as determined by ^{1}H NMR.

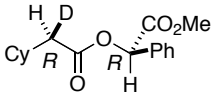
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40-7.27 (m, 5H), 5.04 (d, J = 4.4 Hz, 1H), 4.43 (d, J = 4.5 Hz, 1H), 2.14 (dt, J = 2.0, 6.9 Hz, 1H), 1.90-0.55 (m, 11H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 209.3, 138.1, 129.1, 128.8, 127.7, 80.2, 45.2 (t, J = 19.0 Hz), 34.0, 33.2, 26.2, 26.1, 26.0.
IR (NaCl, thin film): 3458, 2923, 2851, 1711, 1450, 756, 670.
$[\alpha]^{20}_D$ +231.7 (*c* 1.23, $CHCl_3$).



8

A 7 mL glass vial was charged with **7** (60 mg, 0.26 mmol) and lead tetraacetate (115 mg, 0.26 mmol). The vial was purged with nitrogen, CH_2Cl_2 (2.5 mL, saturated with nitrogen) was added. The reaction mixture was stirred 8 h at room temperature, and the CH_2Cl_2 solution was passed through a dry silica gel column (purged with argon) and eluted with CH_2Cl_2 (saturated with argon) under argon to remove benzaldehyde and other low polarity byproducts. **8** and a minor impurity were eluted with 30% ethylacetate / hexane. Column chromatography with a gradient of 5%-30% EtOAc / hexane afforded **8** (14 mg, 38% yield).

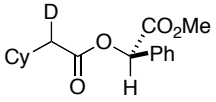
^{1}H NMR (400 MHz, $CDCl_3$, δ): 12.2-11.0 (bs, 1H), 2.21 (bd, J = 6.5 Hz, 1H), 1.85-1.65 (m, 6H), 1.40-0.80 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 180.0, 41.8 (t, J = 19.5 Hz), 34.8, 33.2, 33.1, 26.3, 26.2.
IR (NaCl, thin film): 2925, 2852, 1705, 1414, 1295.



9

Acid **8** (12 mg, 0.084 mmol), methyl-(*R*)-mandelate (21 mg, 0.09 mmol), dicyclohexylcarbodiimide (26 mg, 0.126 mmol), 4-(dimethyl)-aminopyridine (2 mg, 0.016 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and stirred 12 h at room temperature. The crude reaction mixture was filtered through a plug of silica, and the silica was washed with CH_2Cl_2. Column chromatography in 1%-5% EtOAc / hexane afforded **9** (15.6 mg, 52% yield). ^{1}H NMR indicated slight erosion of dr (> 90:10) at the deuterated stereocenter as compared to ^{2}H-**6g** before conversion to **9**. The deuterated stereocenter was assigned to be of the *R* configuration, according to the method of Parker,[10] and the analysis was consistent with Fleming's result.[11] (Refer to ^{1}H NMRs of **^{1}H-9**, **9** and (+/–)-**9** for comparison of chemical shifts).

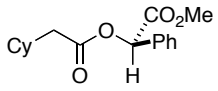
^{1}H NMR (400 MHz, C_6D_6, δ): 7.48 (d, *J* = 6.9 Hz, 2H), 7.07 (t, *J* = 6.0 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.10 (s, 1H), 3.18 (s, 3H), 2.20 (dt, *J* = 1.7, 6.9 Hz, 1H), 1.92-1.80 (m, 1H), 1.80 -1.68 (m, 2H), 1.61-1.42 (m, 3H), 1.22-1.07 (m, 2H), 1.07-0.91 (m, 1H), 0.90-0.75 (m, 2H).
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50-7.40 (m, 2H), 7.44-7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (bd, *J* = 6.9 Hz, 1H), 1.90-1.60 (m, 6H), 1.55-0.90 (m, 5H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, *J* = 20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2.
IR (NaCl, thin film): 2924, 2851, 1760, 1743, 1450, 1436, 1216, 1163.
$[\alpha]^{20}_D$ +112.0 (*c* 1.25, $CHCl_3$)



(+/–)-**9**

Prepared using the same method as **9** except that (±)-**5b** was used to give a 1:1 mixture of diastereomers of **9**.

^{1}H NMR (400 MHz, C_6D_6, δ): 7.48 (d, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.0 Hz, 2H), 7.04 (t, *J* = 7.1 Hz, 1H), 6.11 (s, 2H), 3.18 (s, 6H), 2.20 (dt, *J* = 1.8, 6.9 Hz, 1H), 2.12 (dt, *J* = 1.8, 7.1 Hz, 1H), 1.92-1.80 (m, 1H), 1.80-1.68 (m, 2H), 1.61-1.42 (m, 3H), 1.22-1.07 (m, 2H), 1.07-0.91 (m, 1H), 0.90 -0.75 (m, 2H).
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50-7.40 (m, 2H), 7.44-7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (dt, *J* = 1.9, 6.9 Hz, 1H), 2.30 (bd, *J* = 1.8, 7.0 Hz, 1H), 1.90-1.60 (m, 6H), 1.55-0.90 (m, 5H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, *J* = 20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2.
IR (NaCl, thin film): 2923, 1850, 1760, 1742, 1215, 1163.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{21}DO_4Na$, 314.1473; found, 314.1471.



^{1}H-9

Cyclohexylacetic acid (31.3 mg, 0.22 mmol), methyl-(*R*)-mandelate (33.2 mg, 0.2 mmol), dicyclohexylcarbodiimide (61.9 mg, 0.3 mmol) and 4-(dimethylamino)-pyridine (2.4 mg, 0.02 mmol) were mixed together and dissolved in anhydrous CH_2Cl_2 (2 mL). The mixture was stirred 6 h at room temperature. The CH_2Cl_2 solution was filtered through a plug of silica, the silica was washed with CH_2Cl_2. The filtrate was concentrated and column chromatography afforded **^{1}H-9** (45.1 mg, 78% yield).

^{1}H NMR (400 MHz, C_6D_6, δ): 7.46 (d, *J* = 7.2 Hz, 2H), 7.10-7.00 (m, 3H), 6.09 (s, 1H), 3.18 (s, 3H), 2.22 (dd, *J* = 7.1, 14.9 Hz, 1H), 2.12 (dd, *J* = 7.1, 14.9 Hz, 1H), 1.86 (m, 1H), 1.73 (m, 2H), 1.60-1.40 (m, 3H), 1.22-1.10 (m, 2H), 1.10-0.90 (m, 1H), 0.90-0.75 (m, 2H).
^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.50-7.35 (m, 5H), 5.93 (s, 1H), 3.73 (s, 3H), 2.37 (dd, *J* = 7.0, 15.0 Hz, 1H), 2.31 (dd, *J* = 7.0, 14.9 Hz, 1H), 1.92-1.61 (m, 6H), 1.36-0.60 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.6, 169.6, 134.1, 129.4, 128.9, 127.7, 74.4, 52.7, 41.9, 35.0, 33.1, 26.3, 26.2.
IR (NaCl, thin film): 2925, 2852, 1760, 1743, 1450, 1216, 1159, 1114, 1044, 734.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{22}DO_4Na$, 313.1410; found, 313.1400.
$[\alpha]^{20}_D$ –90.3 (*c* 1.03, $CHCl_3$).

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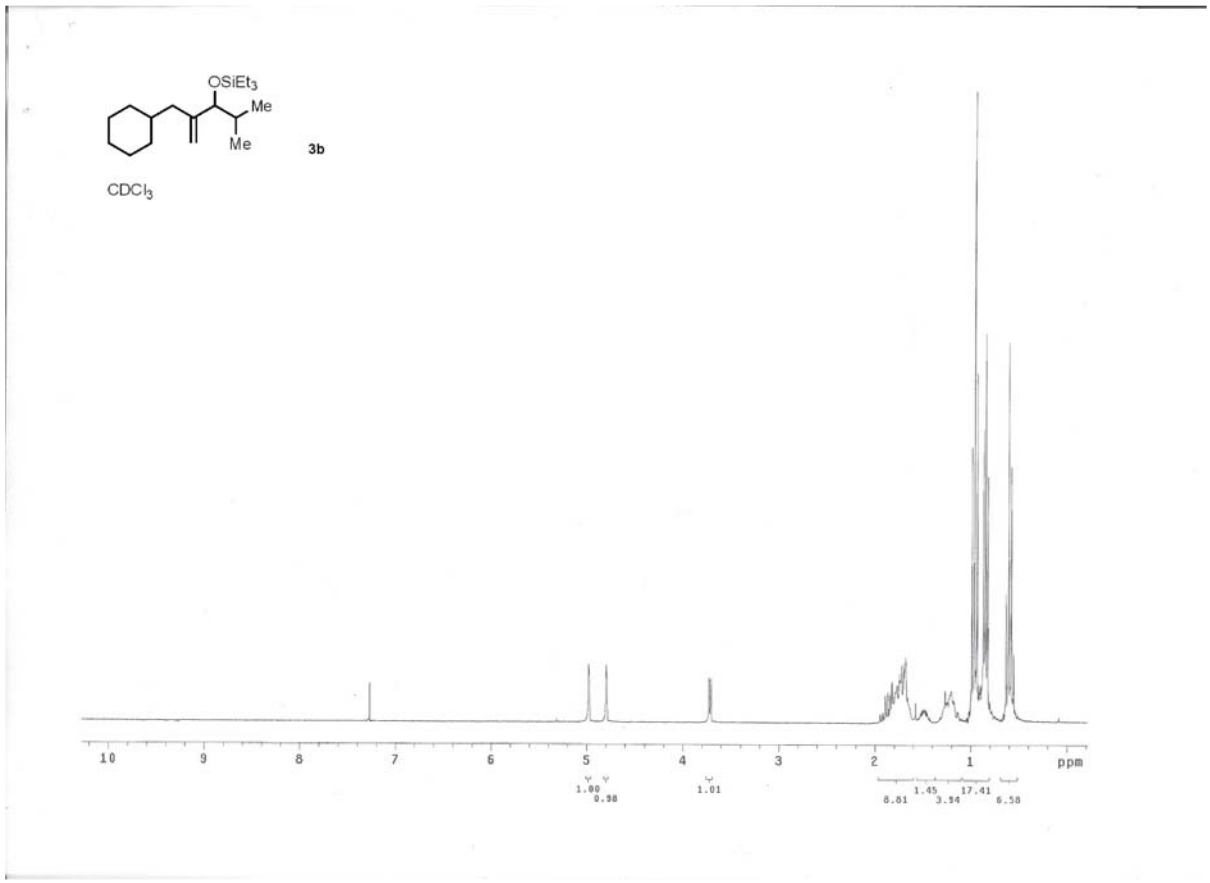
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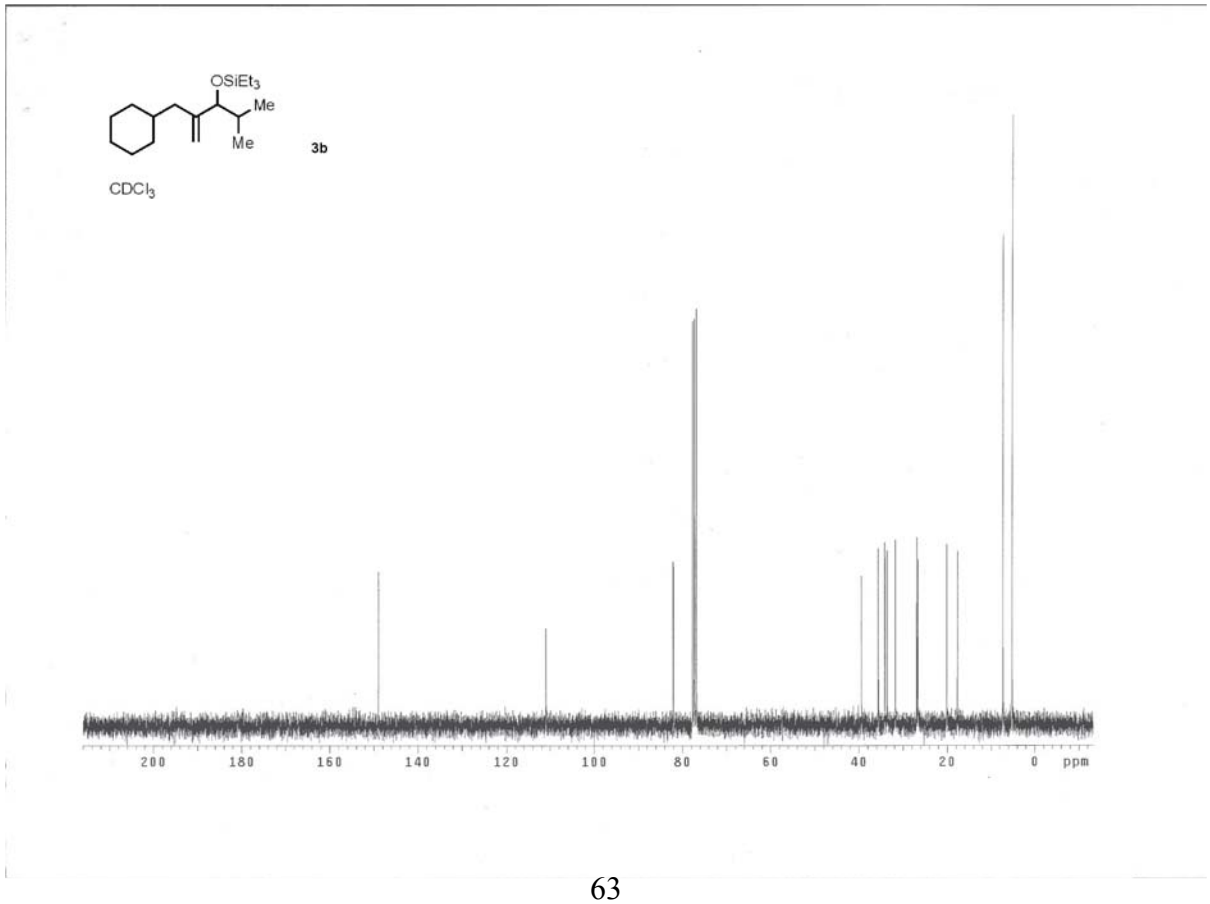
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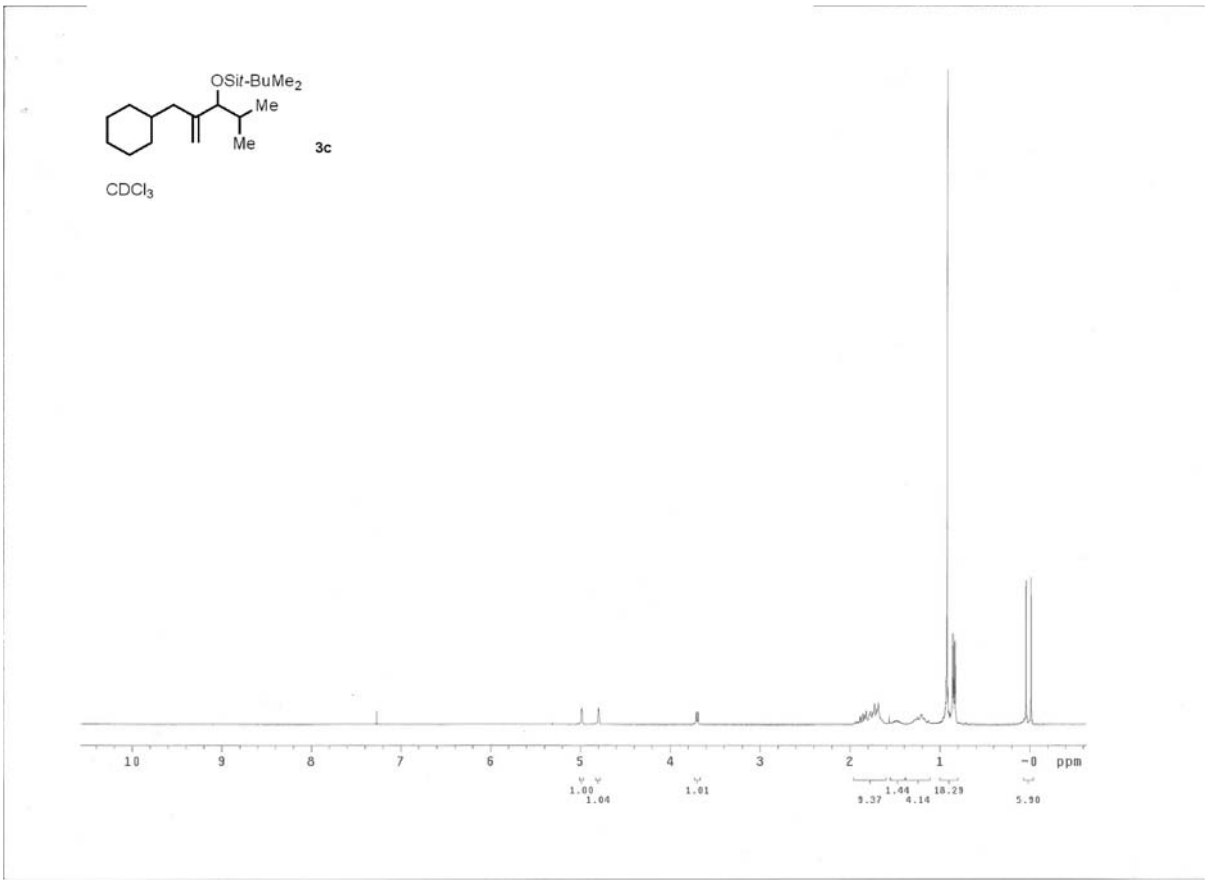
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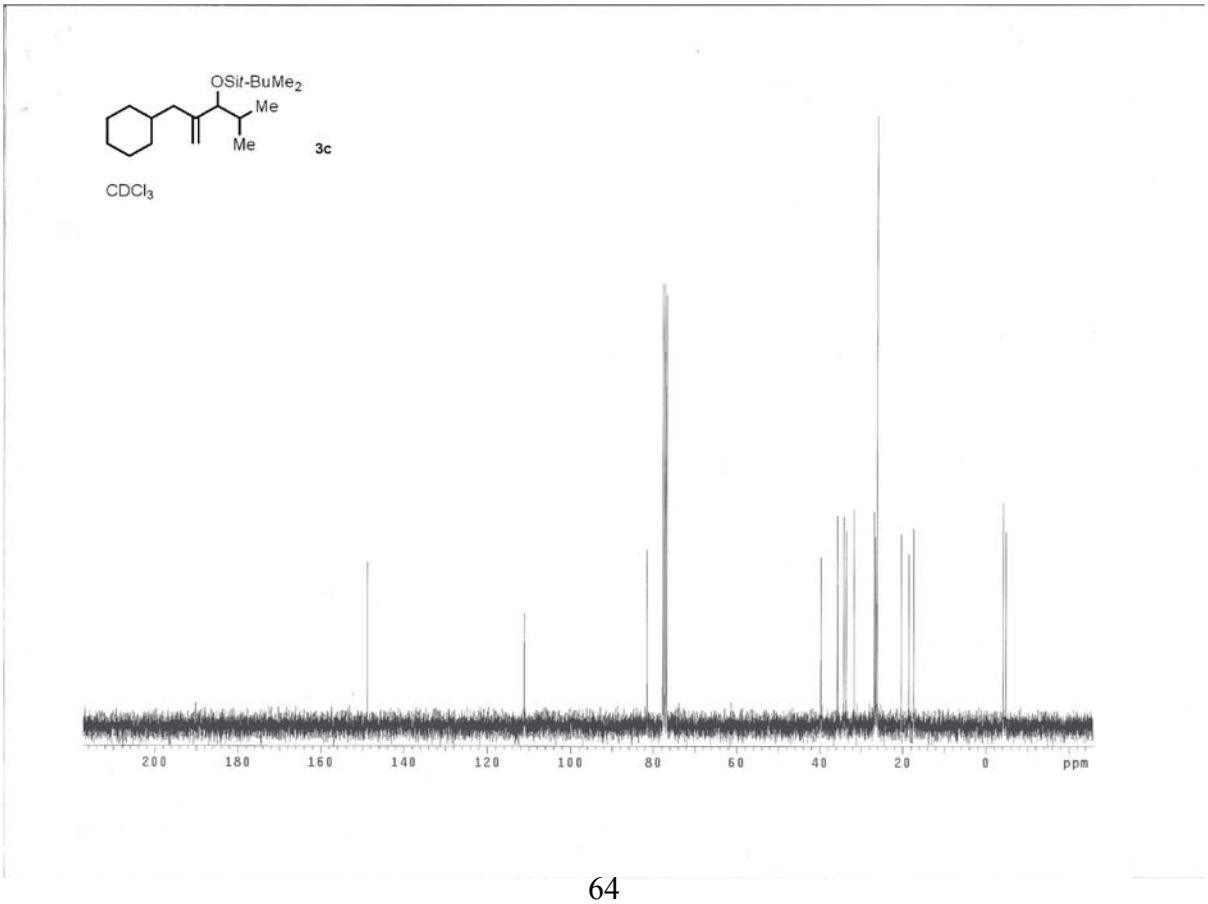
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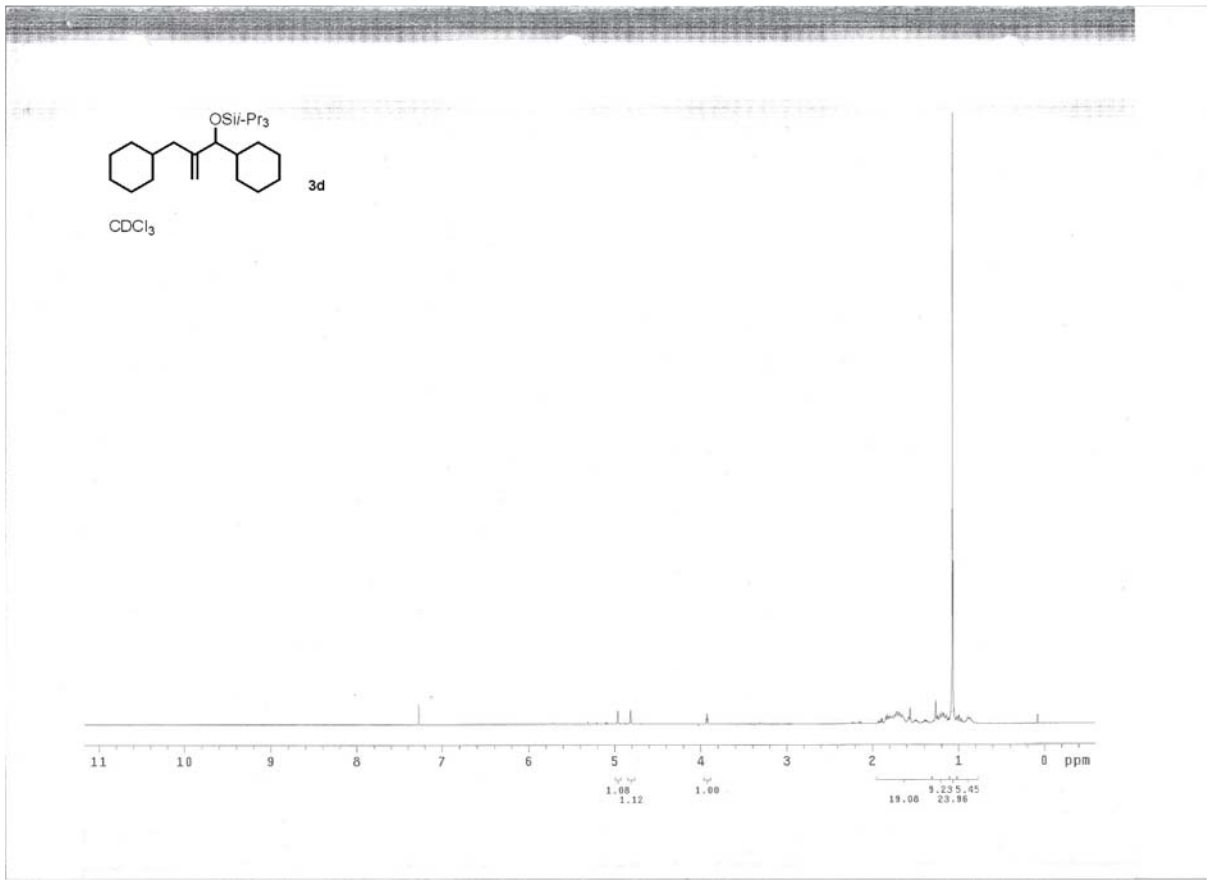
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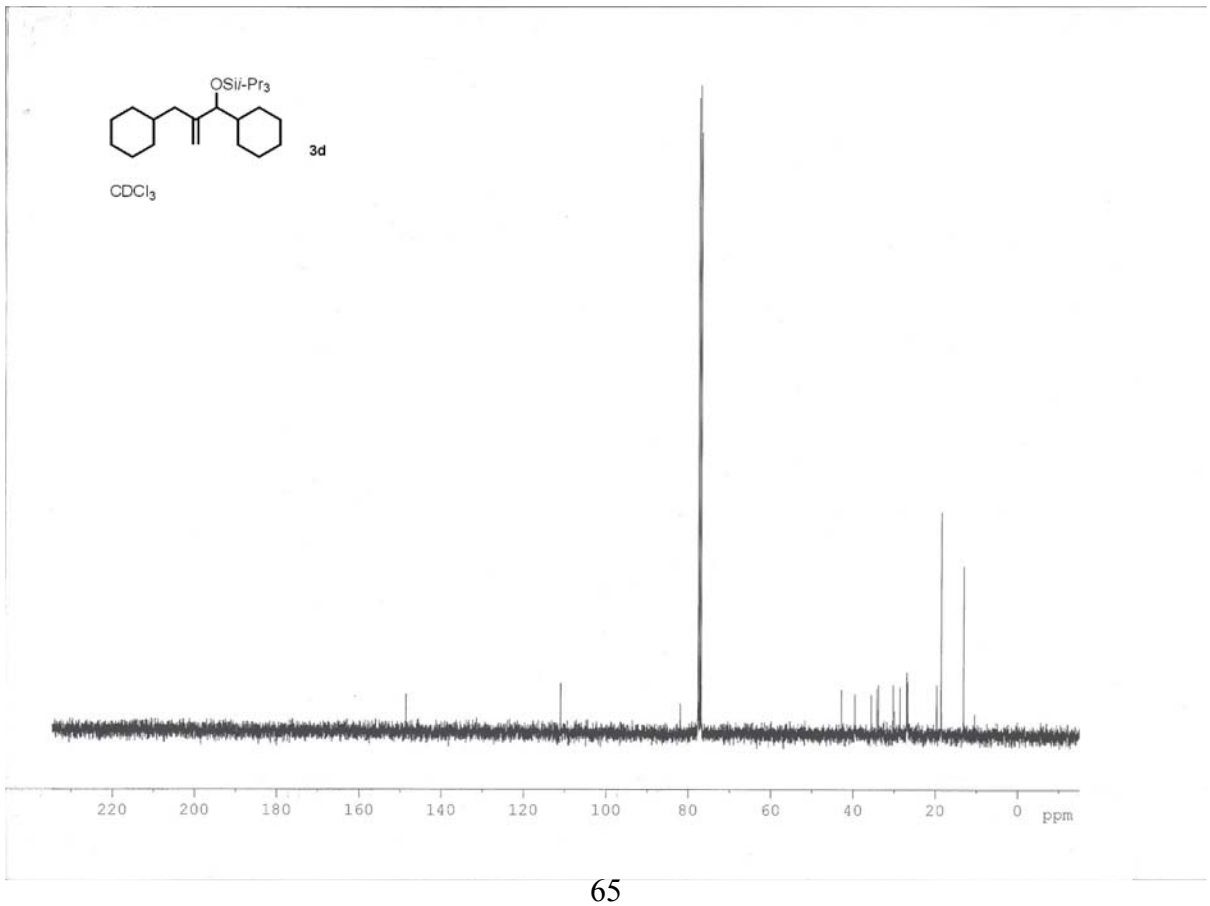
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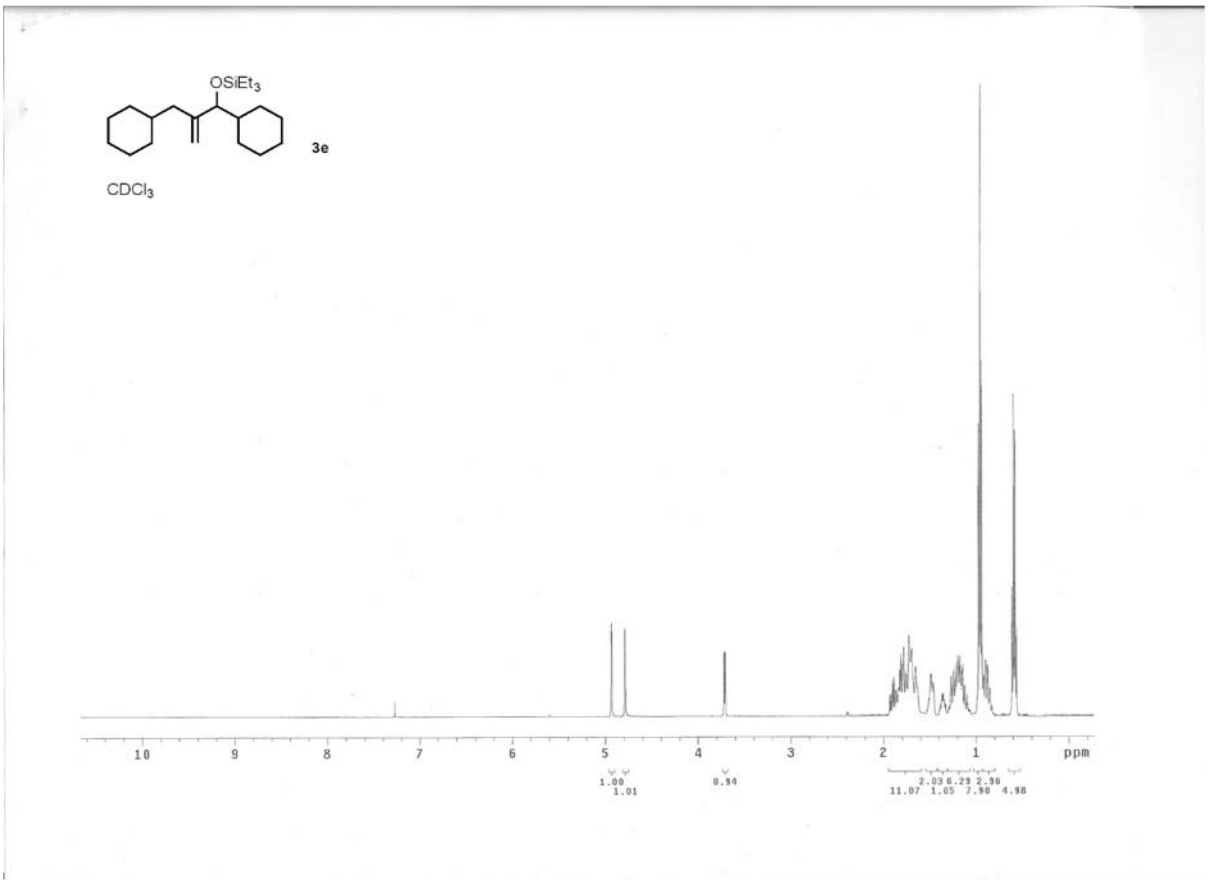
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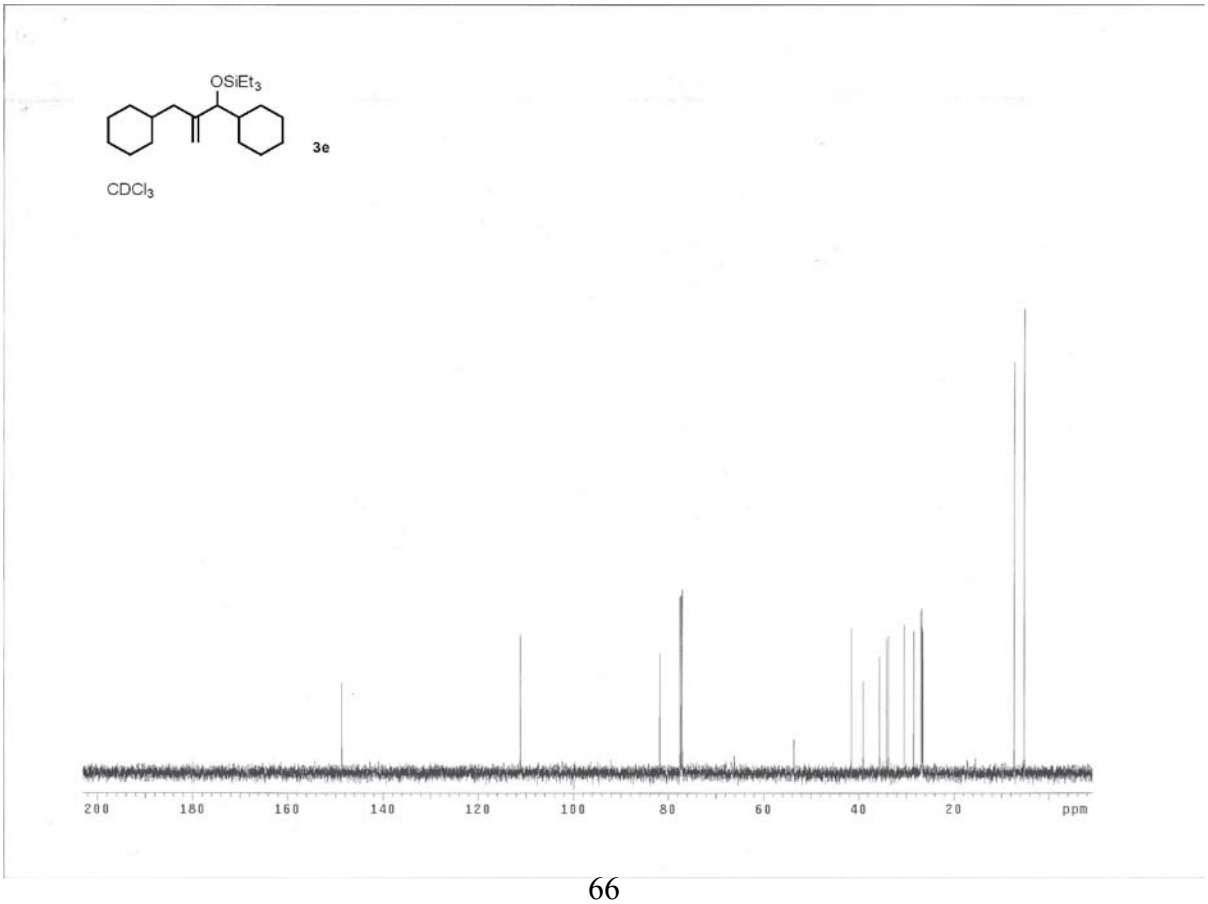
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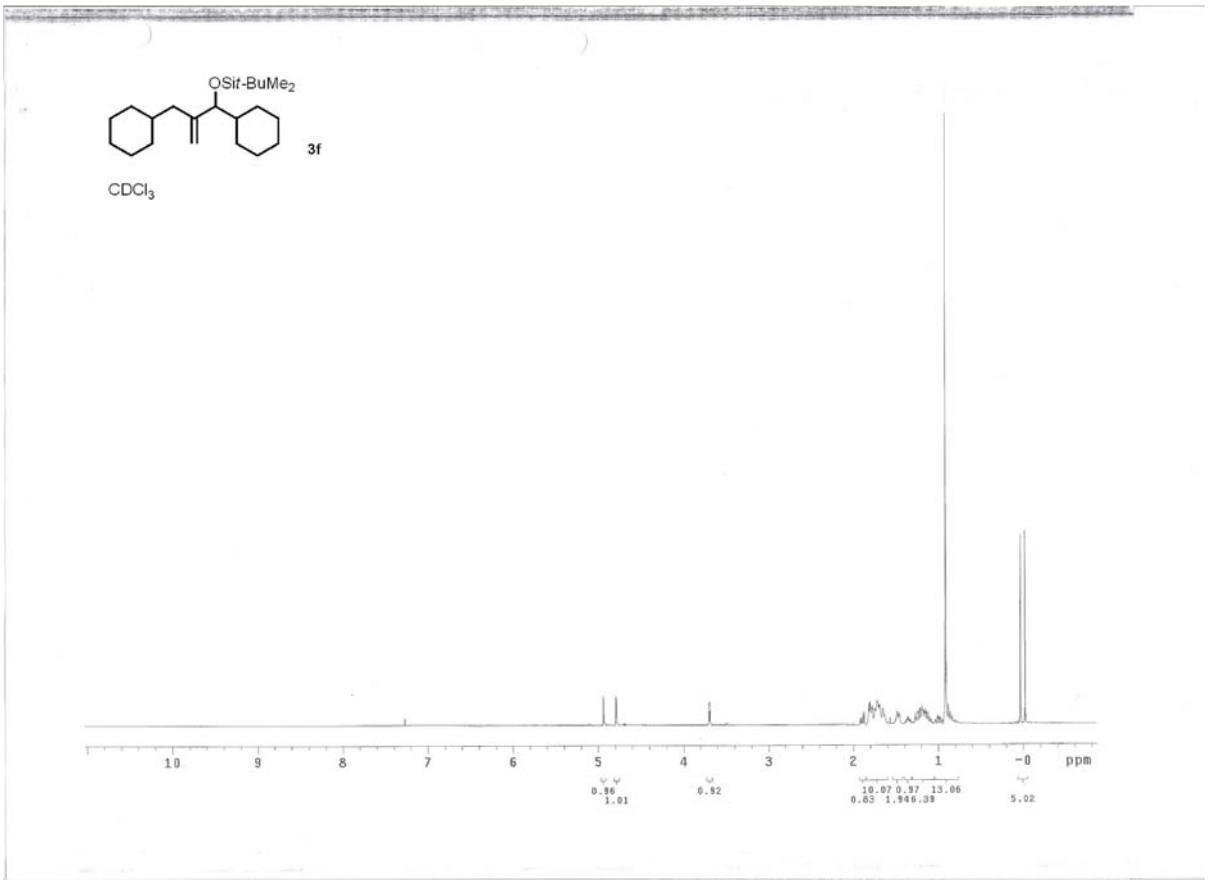
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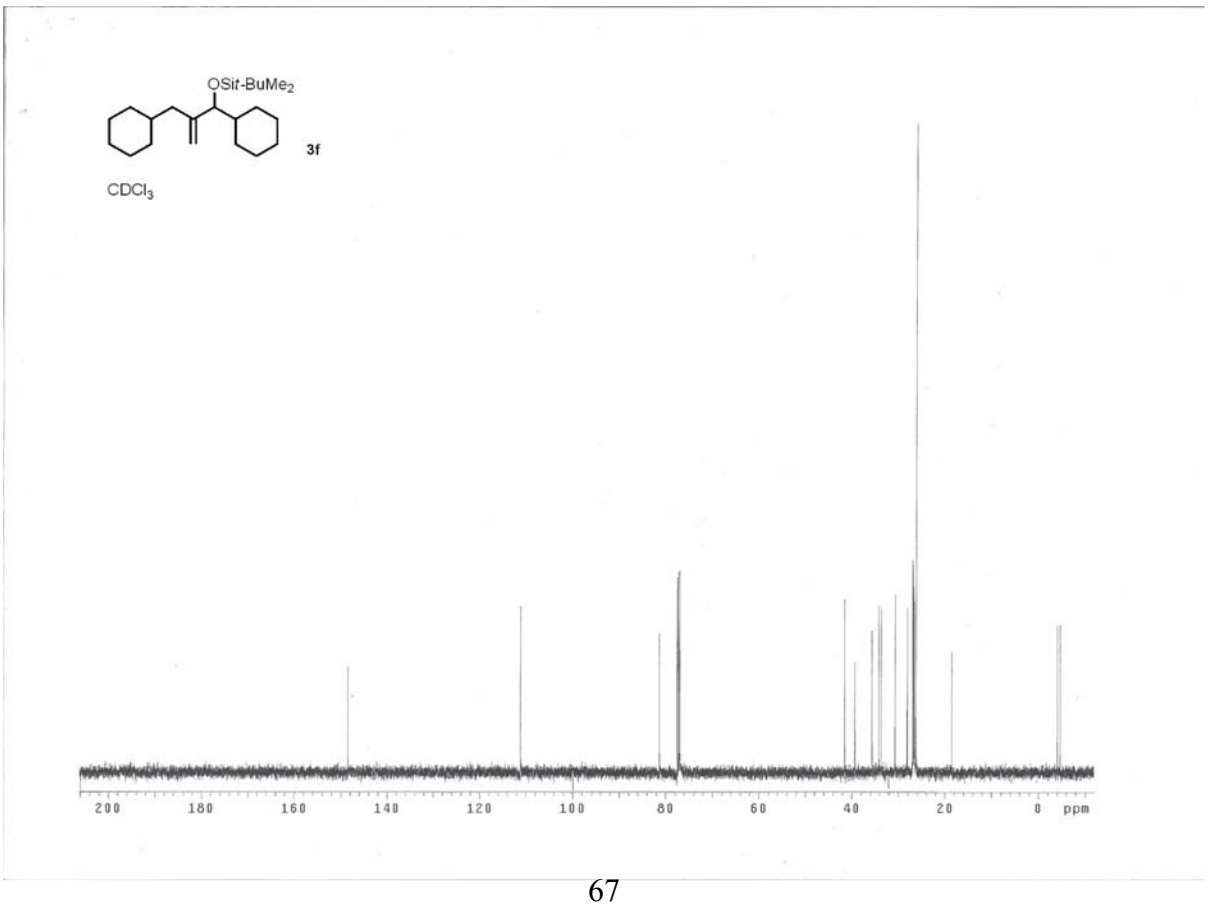
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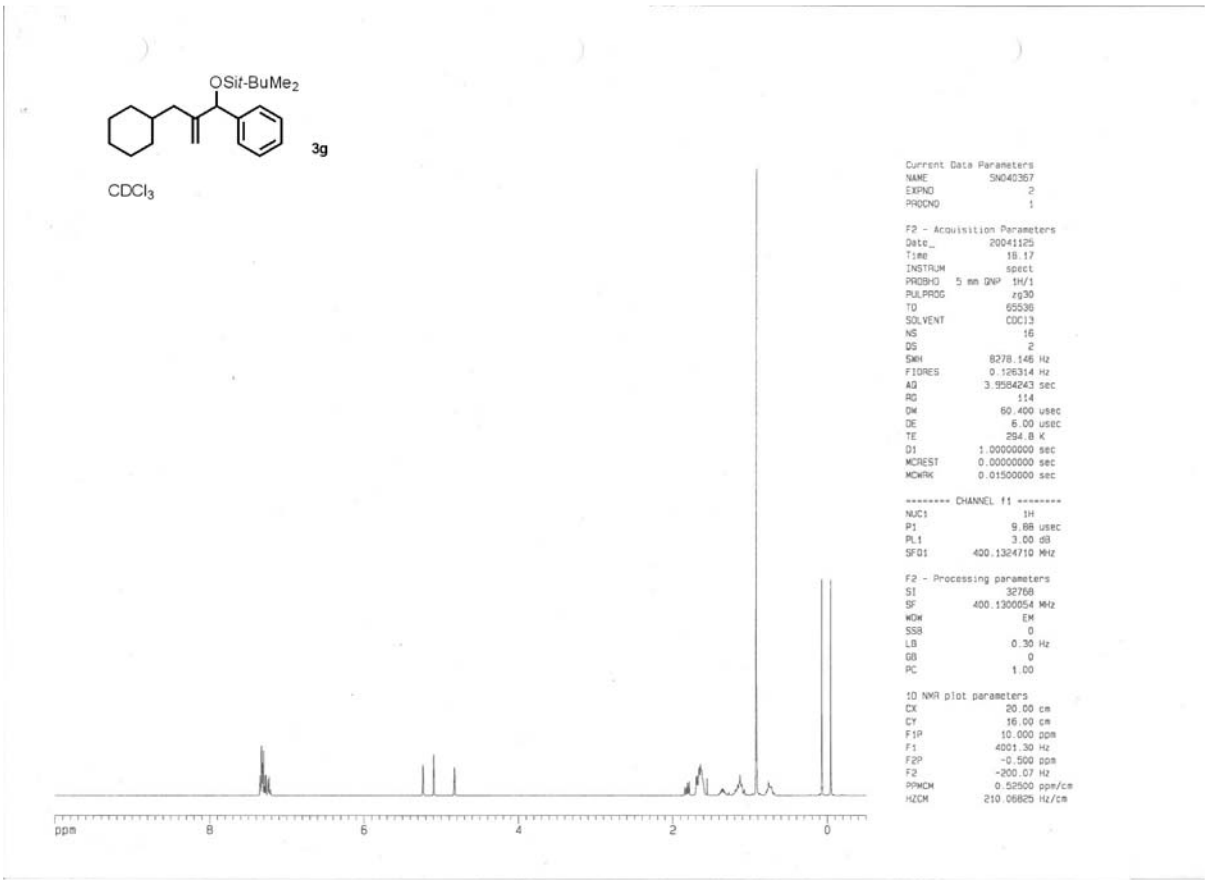


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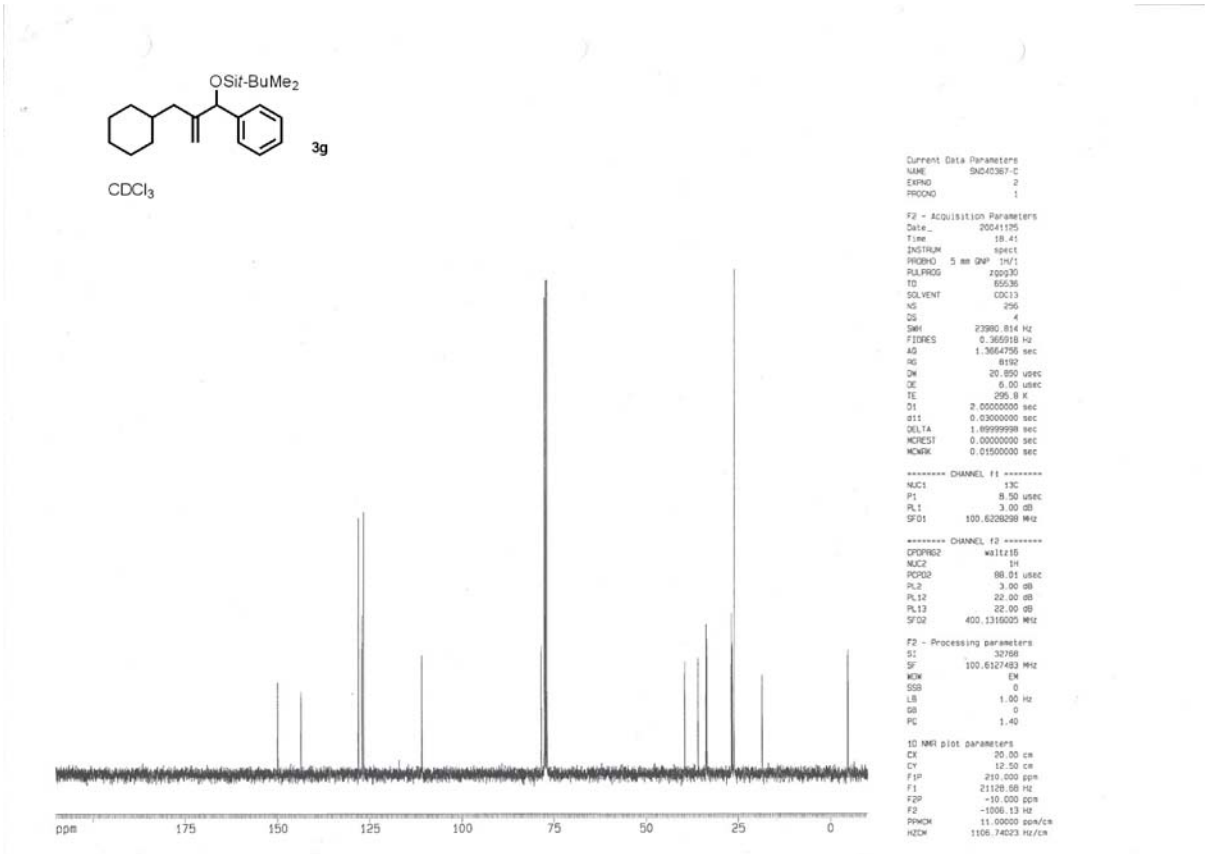


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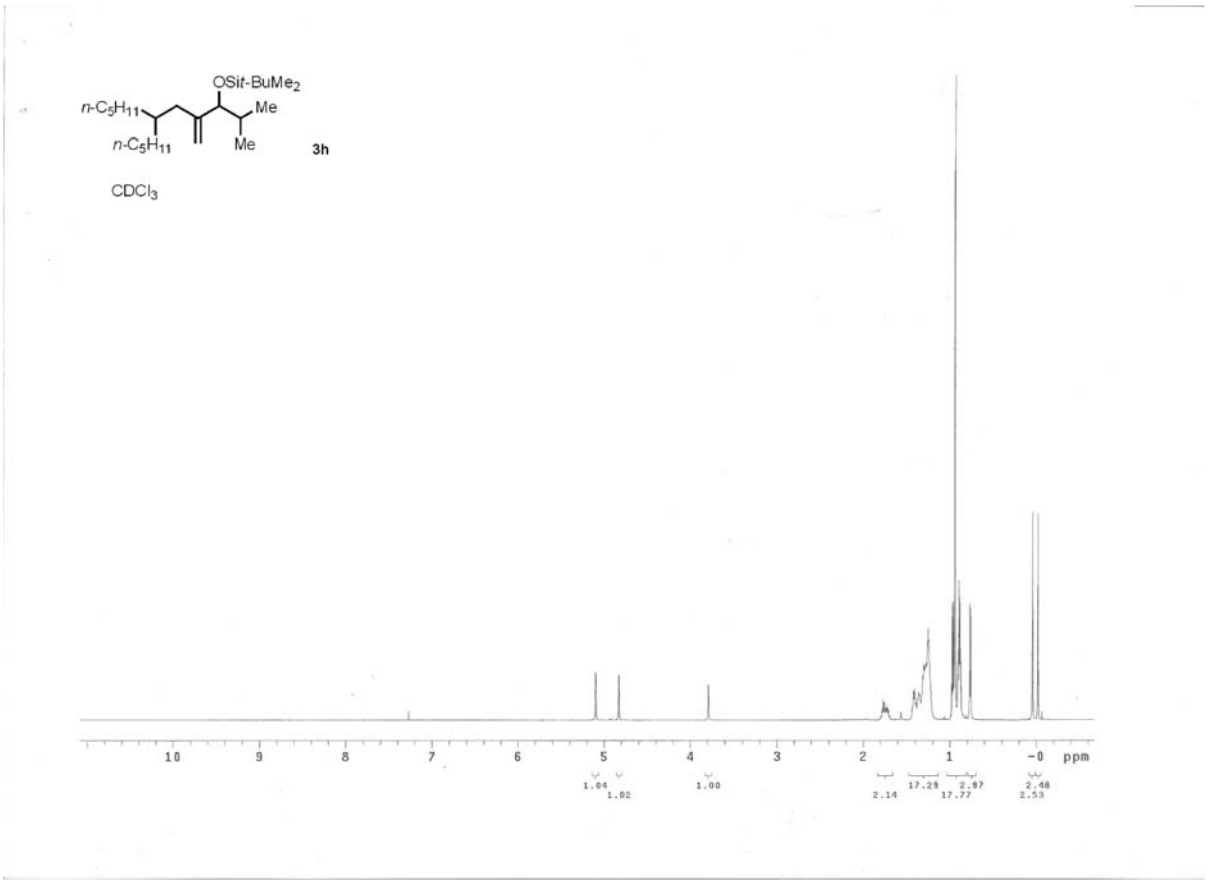
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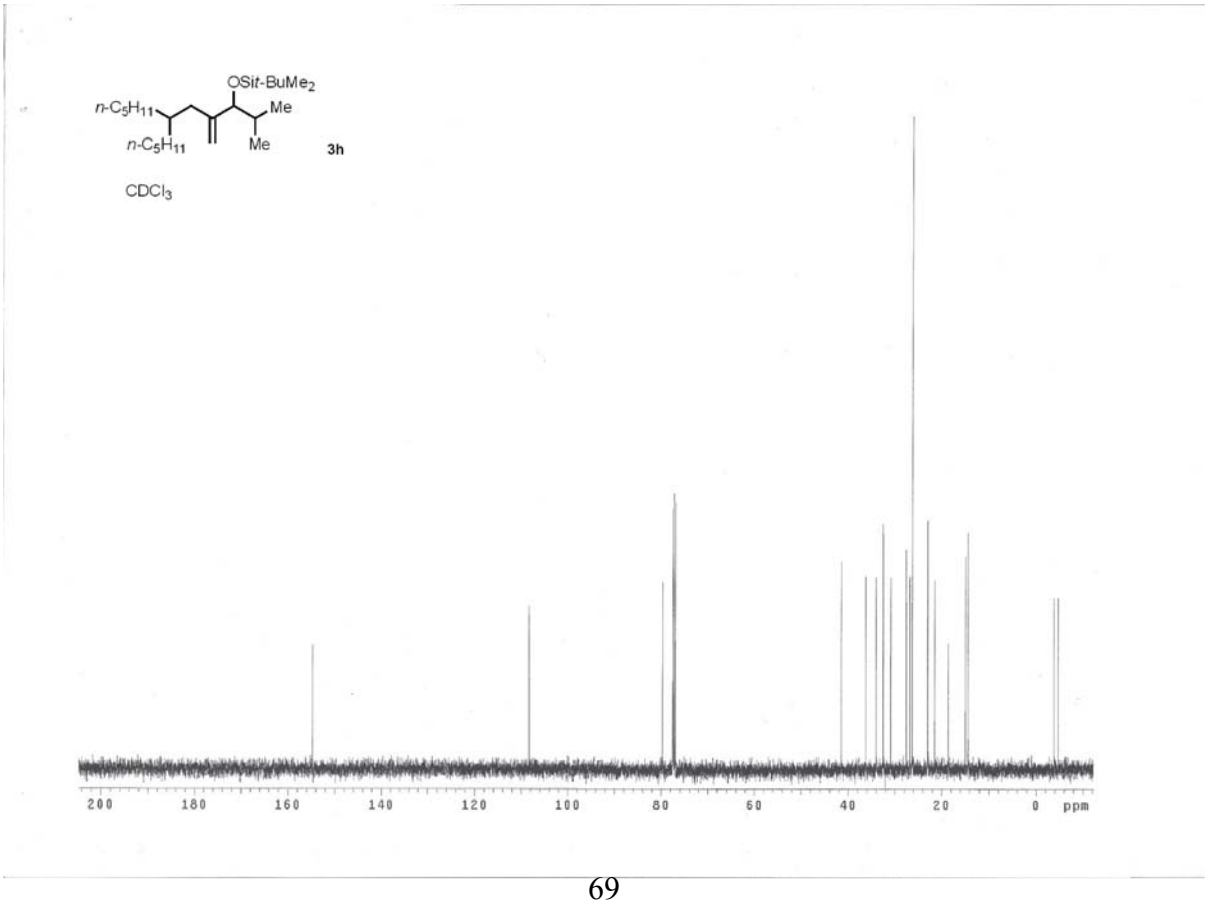
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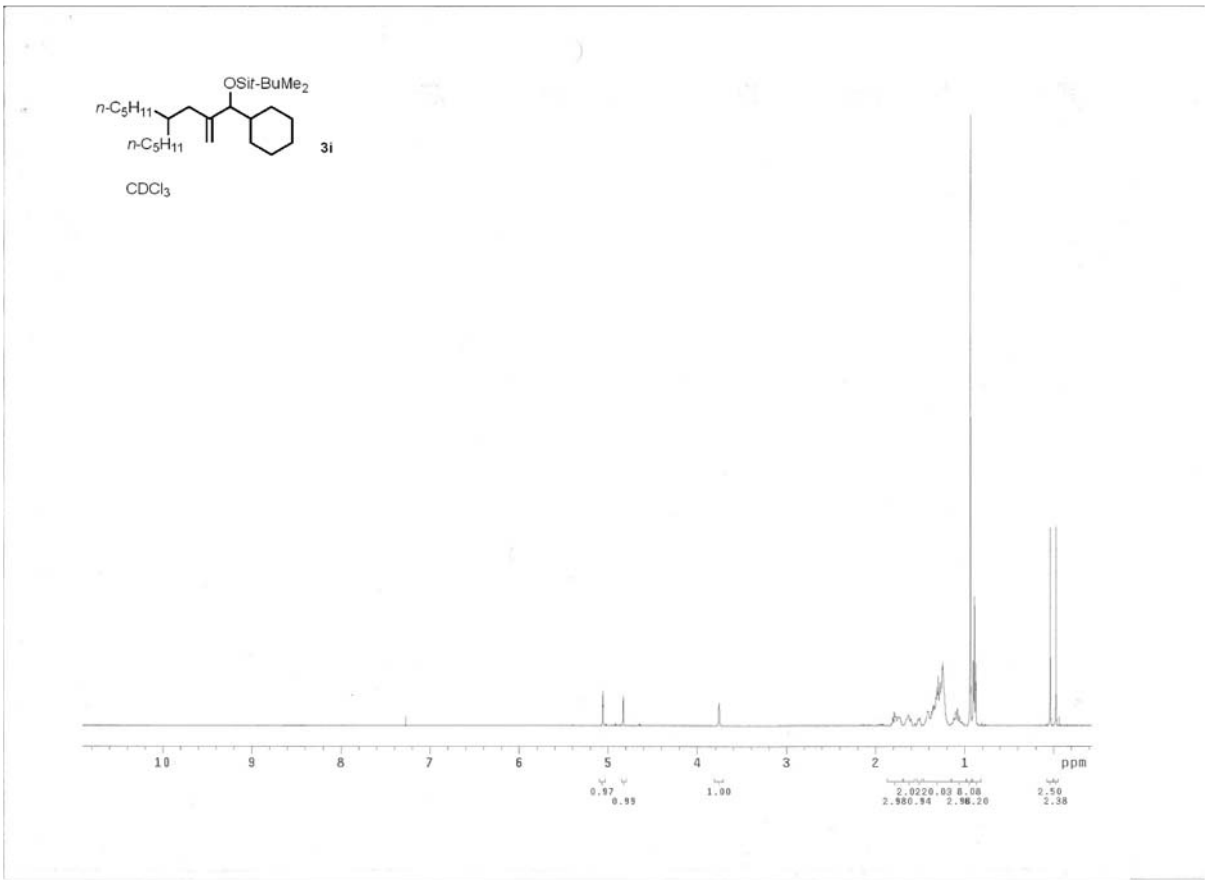
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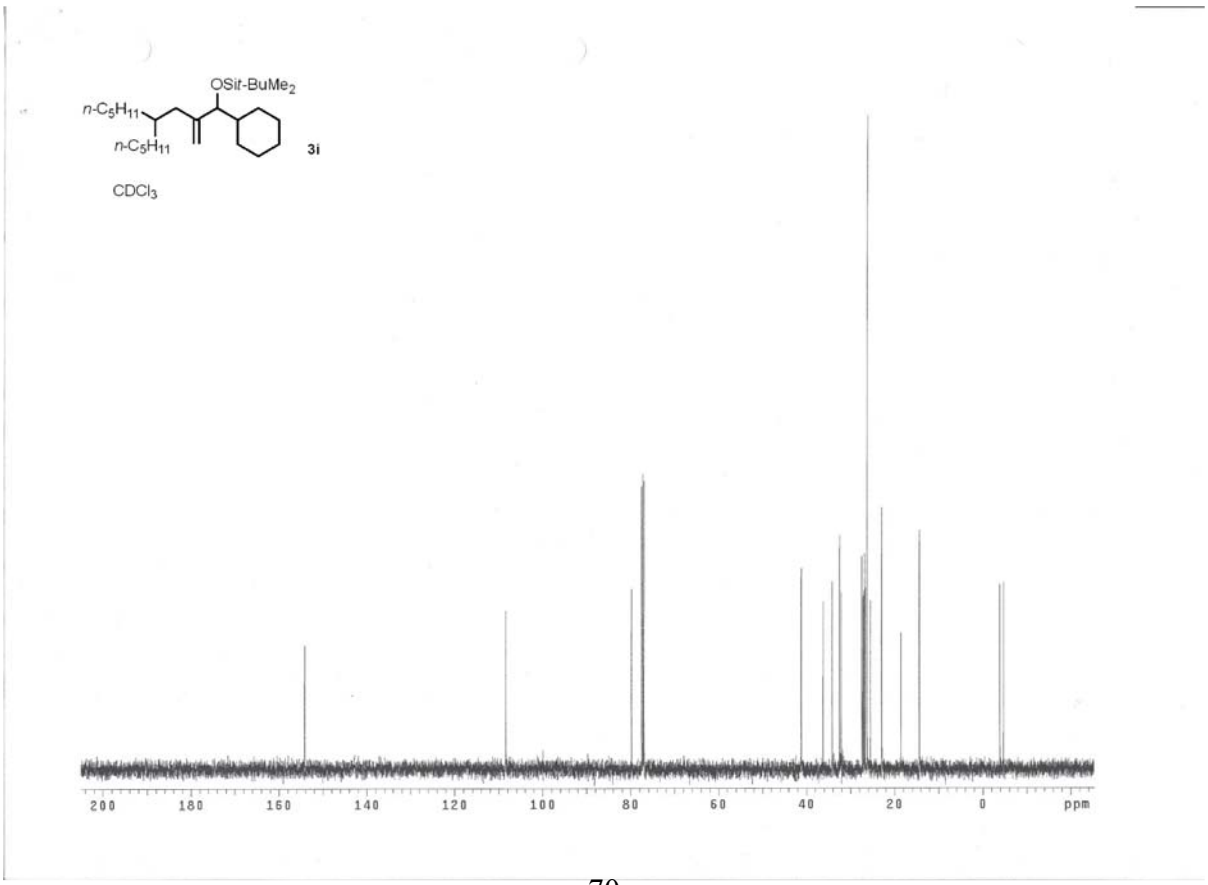
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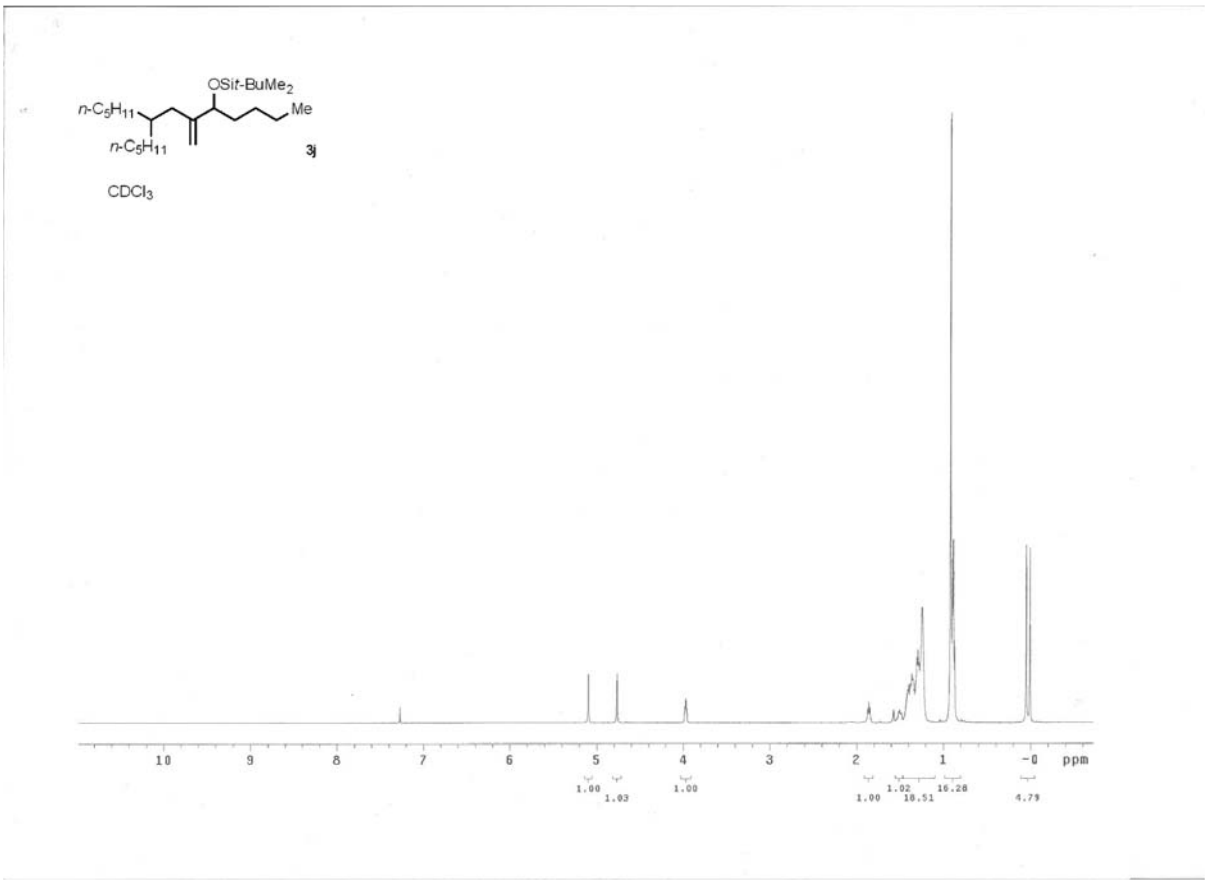
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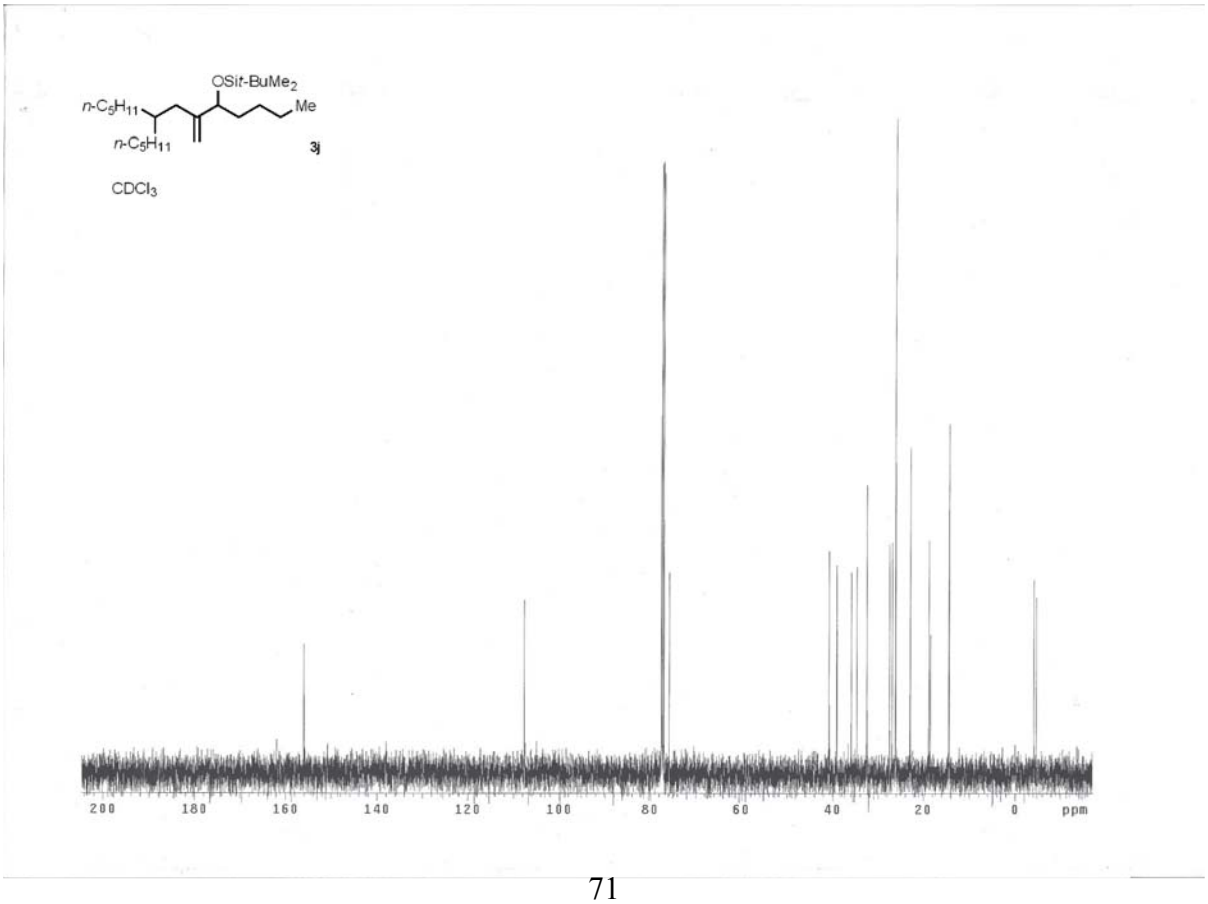
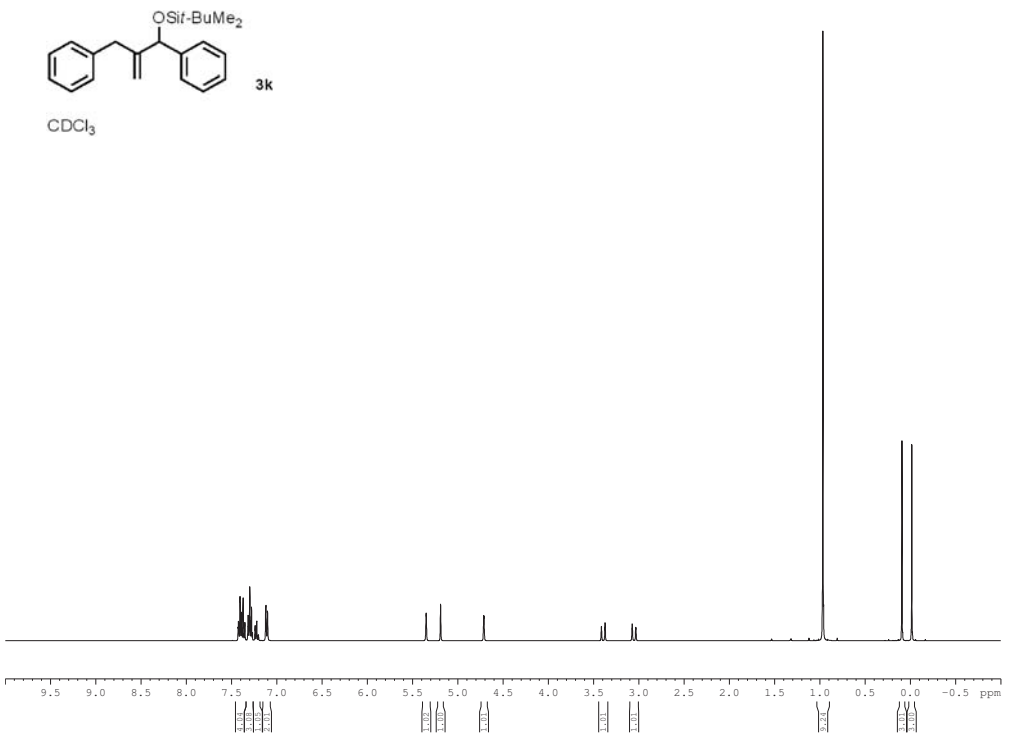
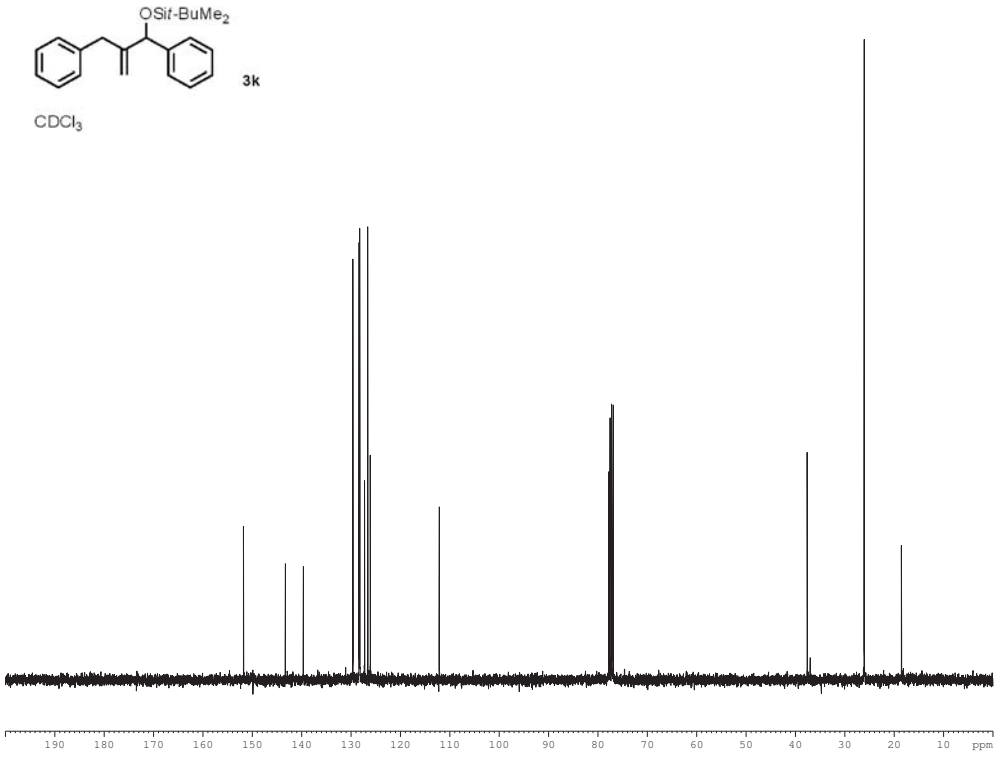
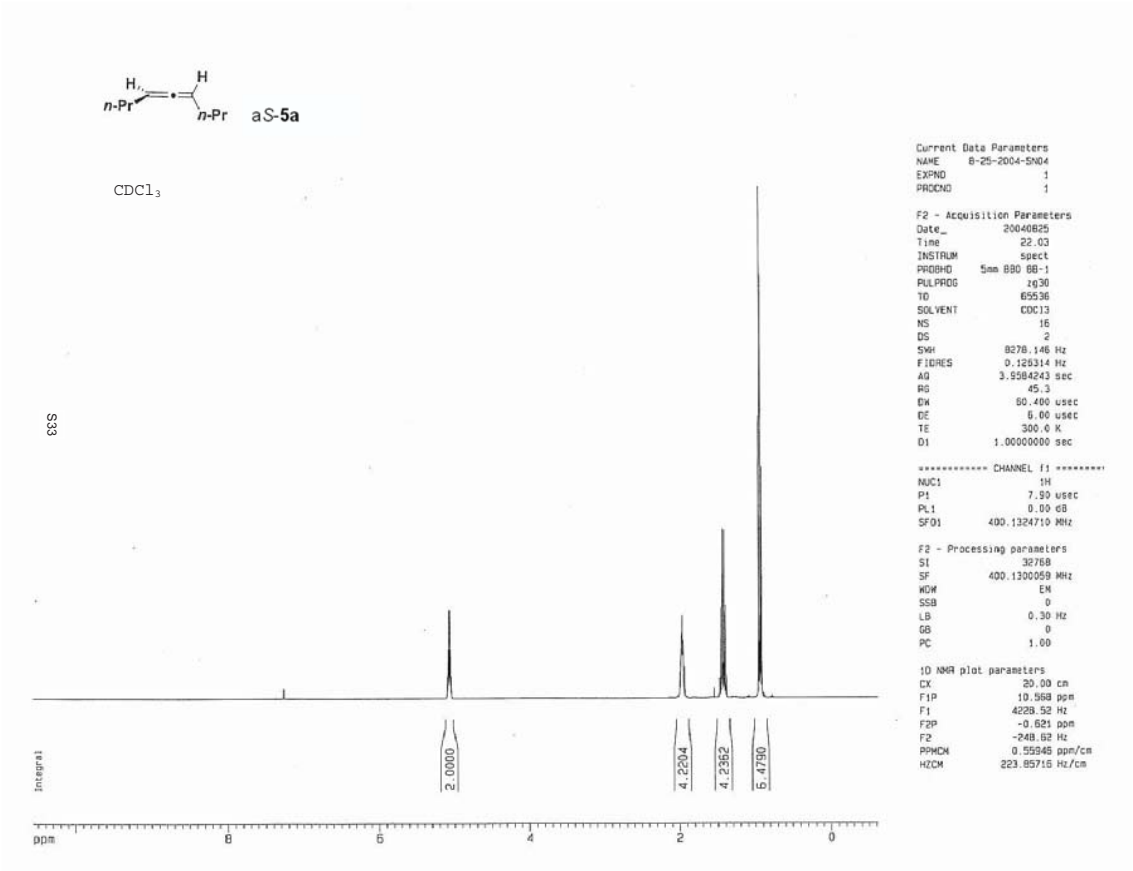
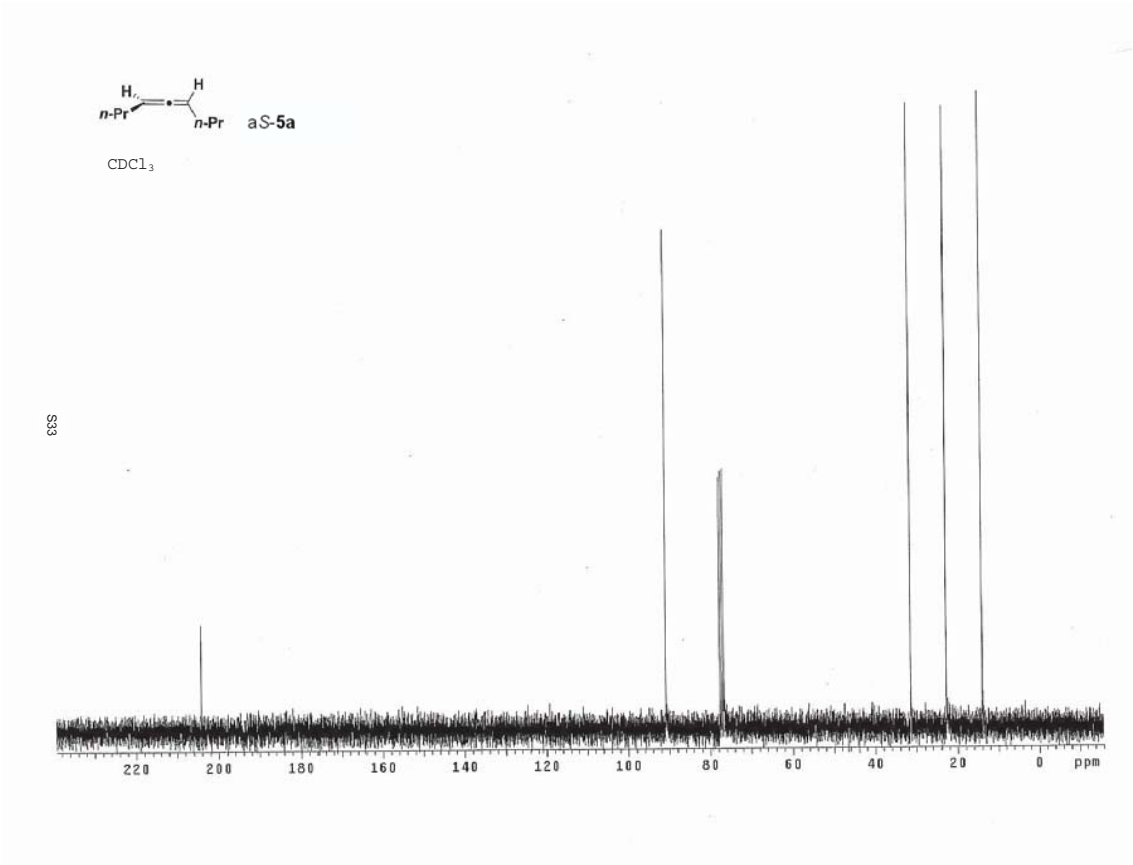
18.51
4.79

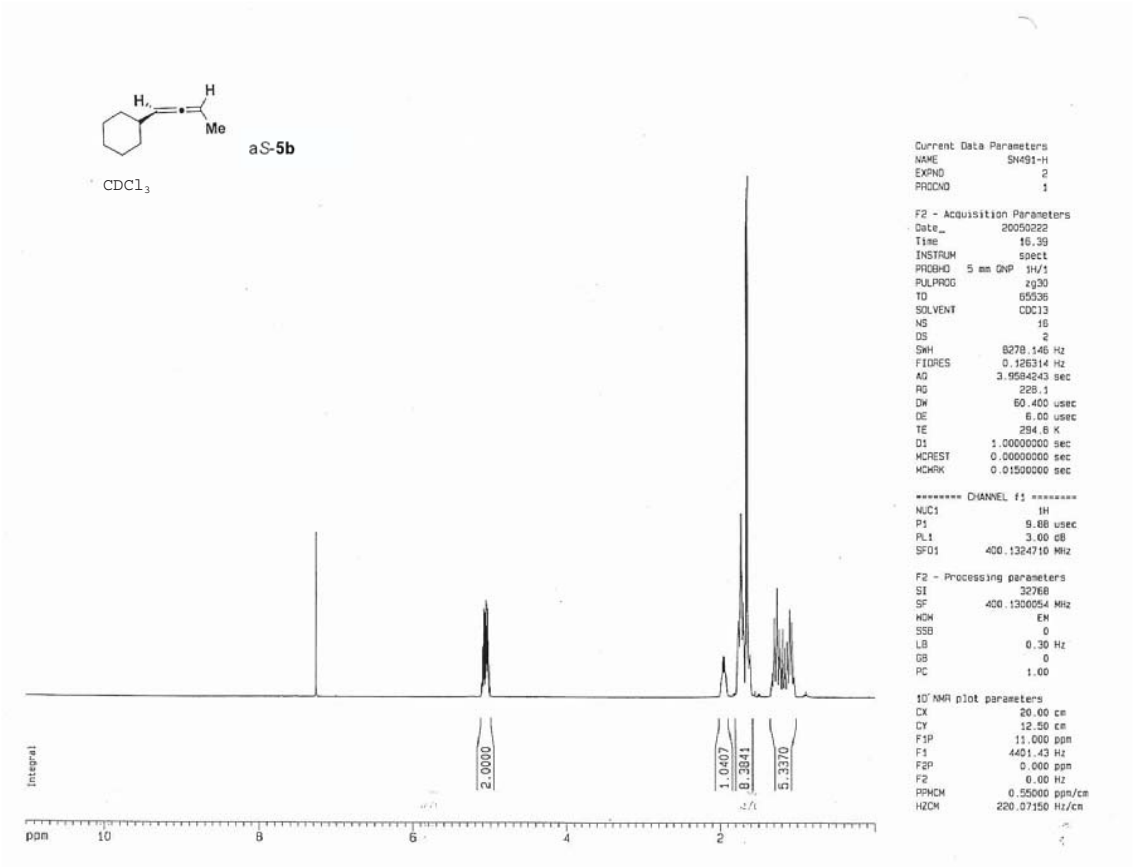

OSi-t-BuMe2
n-C5H11
Me
n-C5H11
3j
CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm

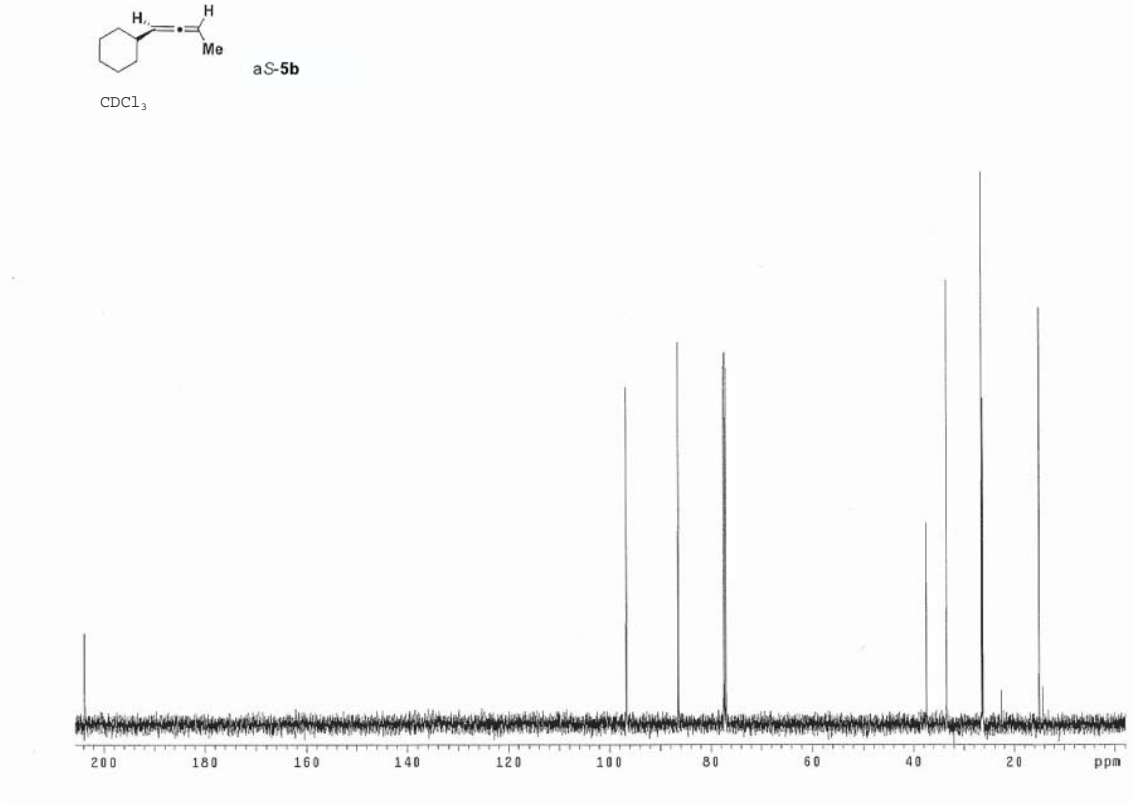

OSi*t*-BuMe$_2$
3k
CDCl$_3$
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

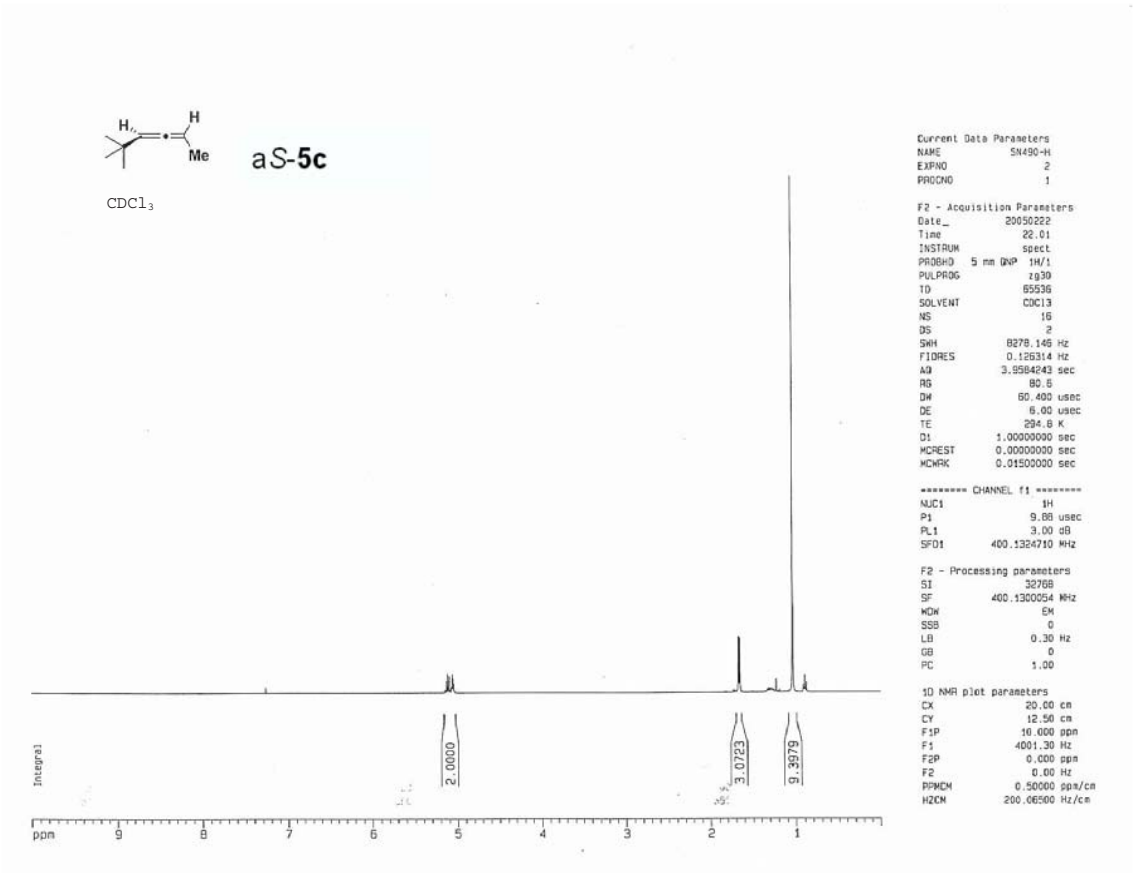

OSi*t*-BuMe$_2$
3k
CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

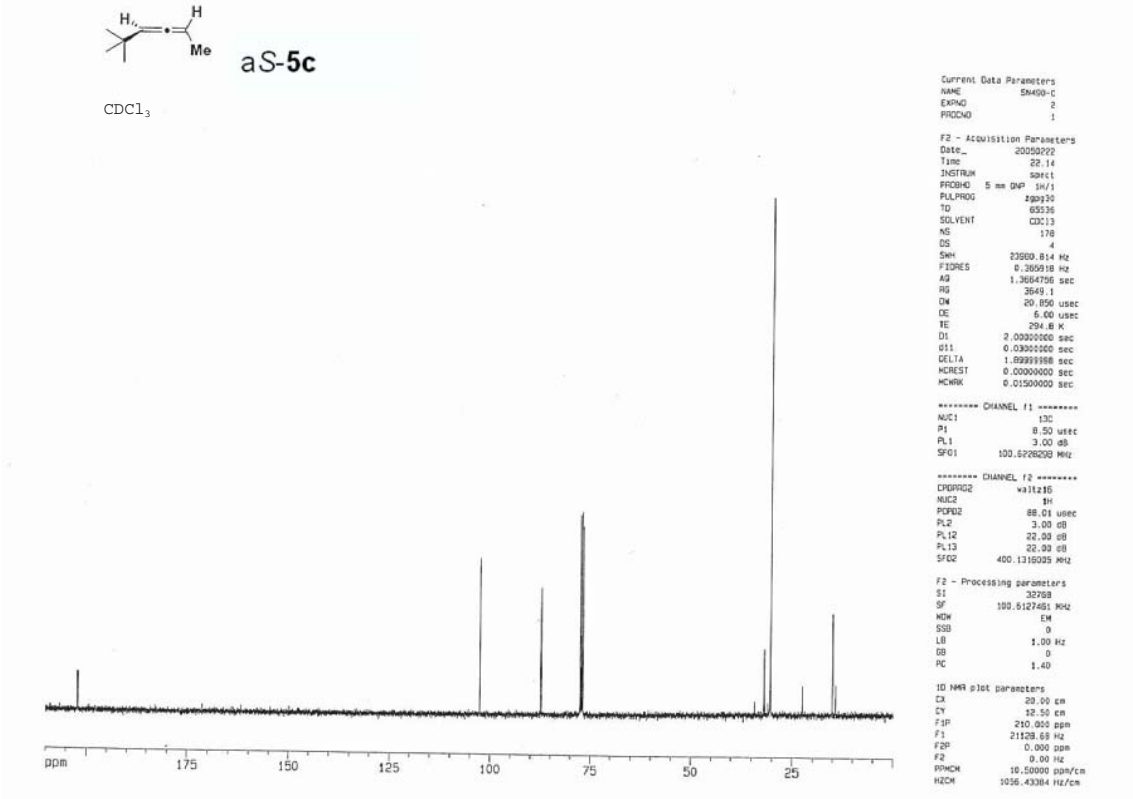

n-Pr
H
n-Pr
aS-5a
CDCl3
S33
Integral
2.0000
4.2204
4.2362
6.4790
ppm
8
6
4
2
0
Current Data Parameters
NAME 8-25-2004-SN04
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20040825
Time 22.03
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 45.3
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300059 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.568 ppm
F1 4228.52 Hz
F2P -0.621 ppm
F2 -248.62 Hz
PPMCM 0.55948 ppm/cm
HZCM 223.85716 Hz/cm

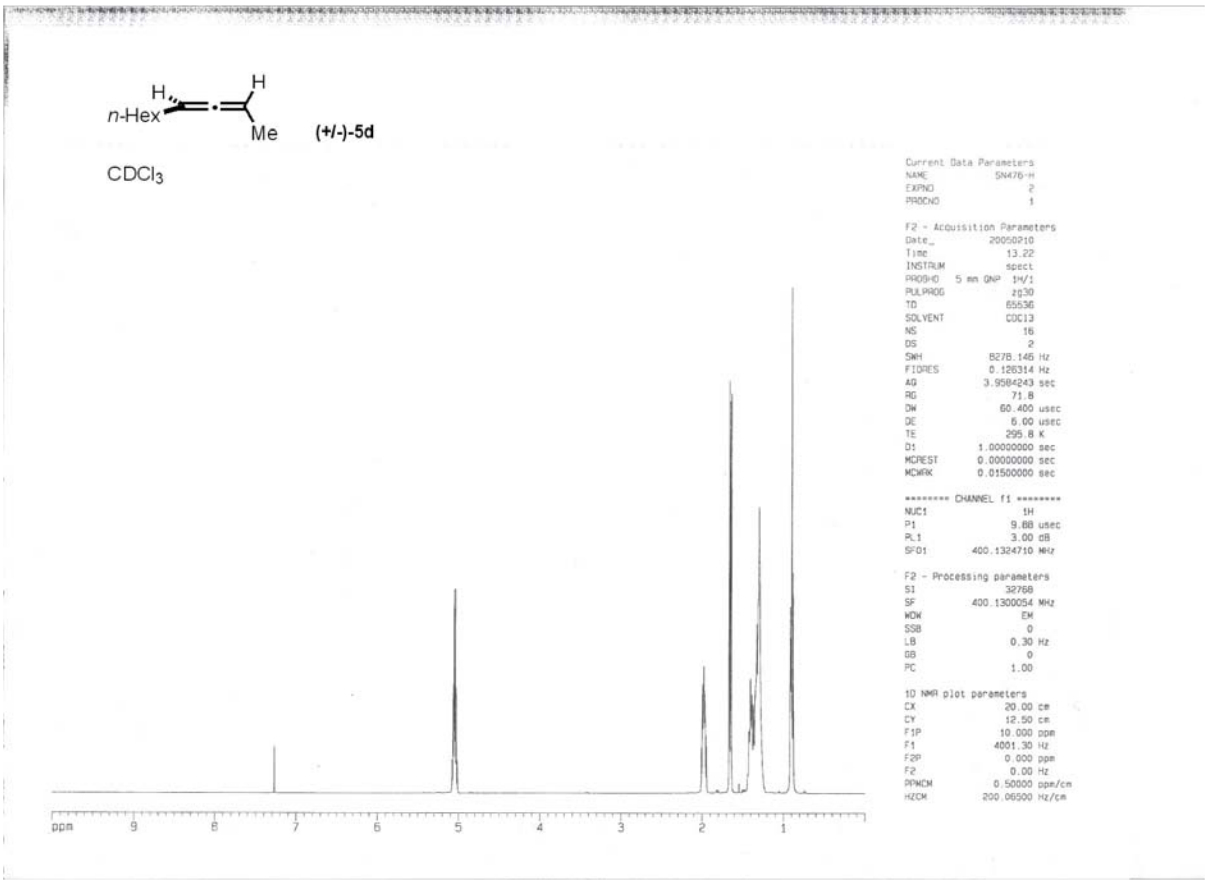

n-Pr
H
n-Pr
aS-5a
CDCl3
S33
220
200
180
160
140
120
100
80
60
40
20
0
ppm


H
H
Me
aS-5b
CDCl3
Current Data Parameters
NAME SN491-H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050222
Time 16.39
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 228.1
DW 60.400 usec
DE 6.00 usec
TE 294.6 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.55000 ppm/cm
HZCM 220.07150 Hz/cm
Integral
2.0000
1.0407
0.3841
5.3370
ppm
10
8
6
4
2


H
H
Me
aS-5b
CDCl3
200
180
160
140
120
100
80
60
40
20
ppm


aS-5c
CDCl3
Current Data Parameters
NAME SN490-H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050222
Time 22.01
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 80.6
DW 60.400 usec
DE 6.00 usec
TE 294.8 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm
Integral
2.0000
3.0723
9.3979
ppm
9
8
7
6
5
4
3
2
1


aS-5c
CDCl3
Current Data Parameters
NAME SN490-C
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050222
Time 22.14
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 178
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3684756 sec
RG 3649.1
DW 20.850 usec
DE 6.00 usec
TE 294.8 K
D1 2.00000000 sec
D11 0.03000000 sec
DELTA 1.89999988 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 3.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 88.01 usec
PL2 3.00 dB
PL12 22.00 dB
PL13 22.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127461 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 210.000 ppm
F1 21128.68 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.50000 ppm/cm
HZCM 1056.43384 Hz/cm
ppm
175
150
125
100
75
50
25



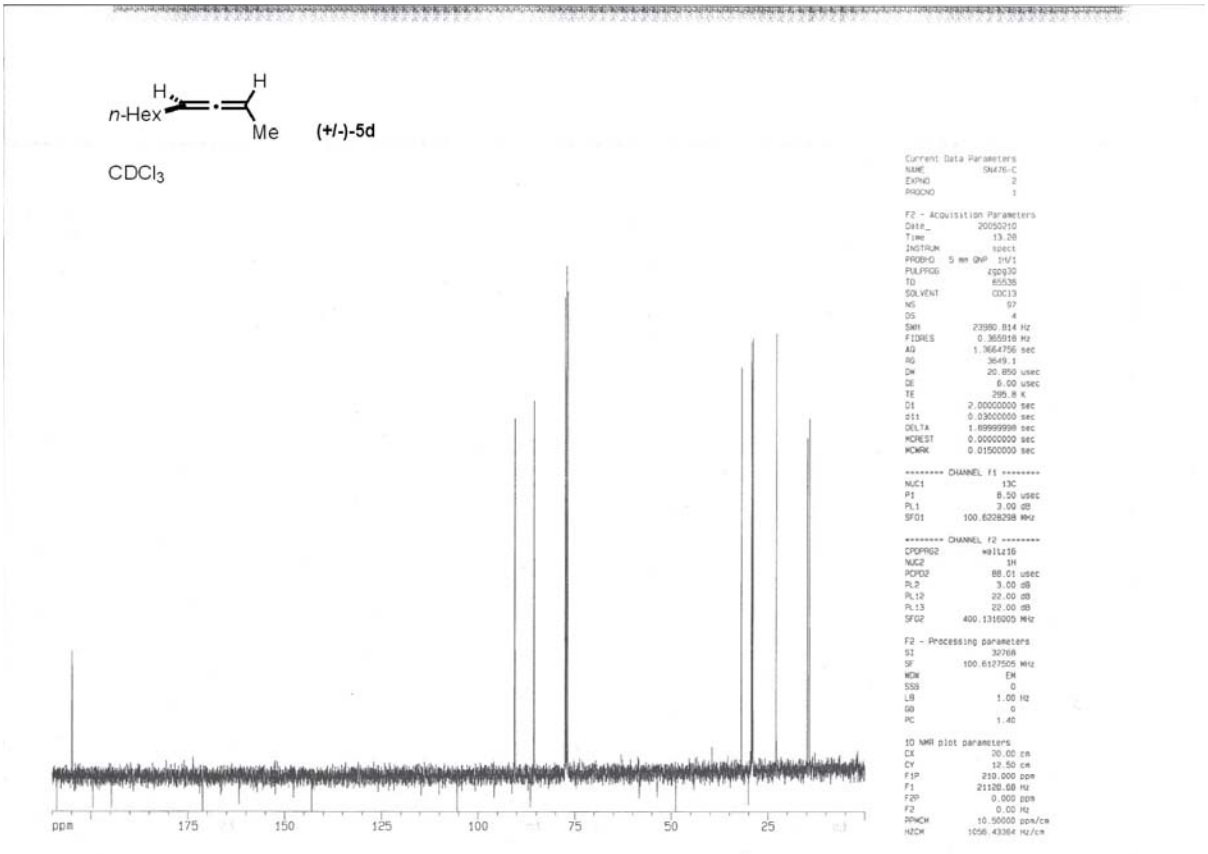
Current Data Parameters
NAME SN476-H
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050210
Time 13.22
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 71.8
DW 60.400 usec
DE 6.00 usec
TE 295.8 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm



Current Data Parameters
NAME SN476-C
EXPNO 2
PROCNO 1

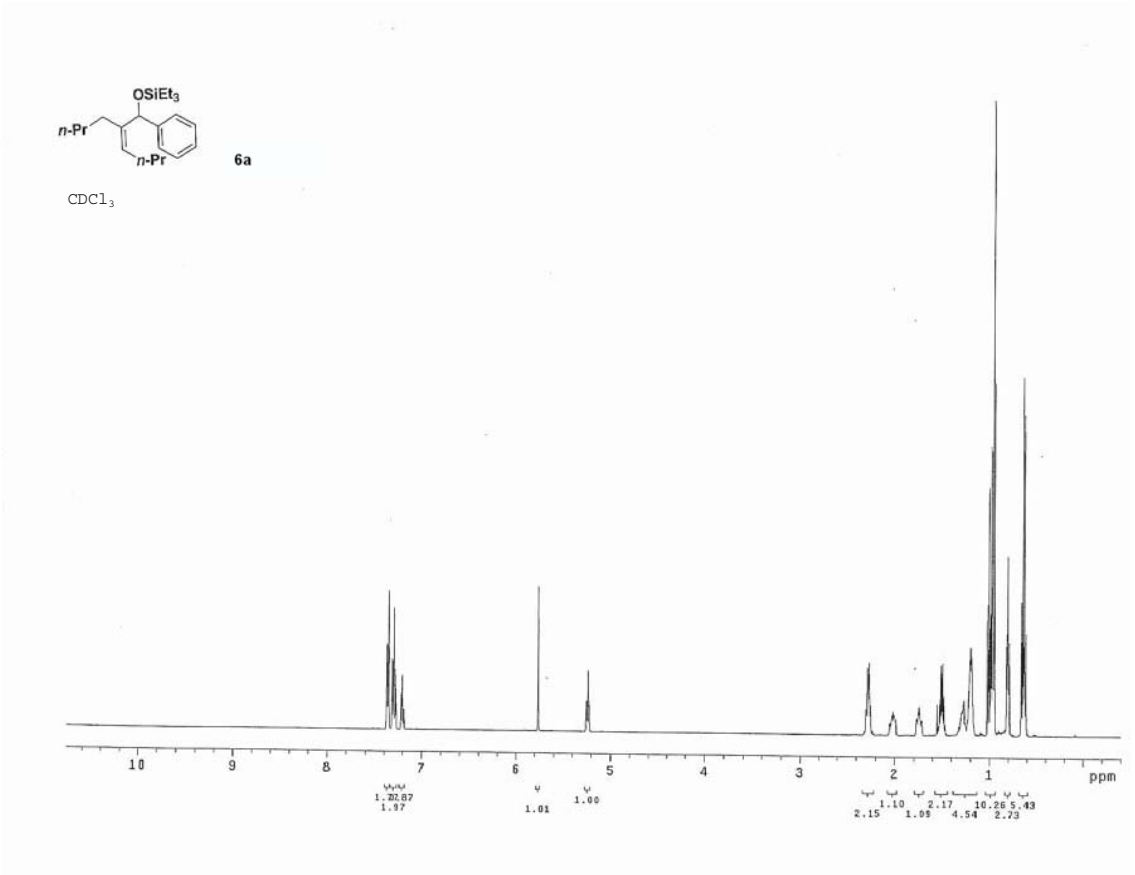
F2 - Acquisition Parameters
Date_ 20050210
Time 13.28
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 97
DS 4
SWH 23980.814 Hz
FIDRES 0.365818 Hz
AQ 1.3664756 sec
RG 3649.1
DW 20.850 usec
DE 6.00 usec
TE 295.8 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

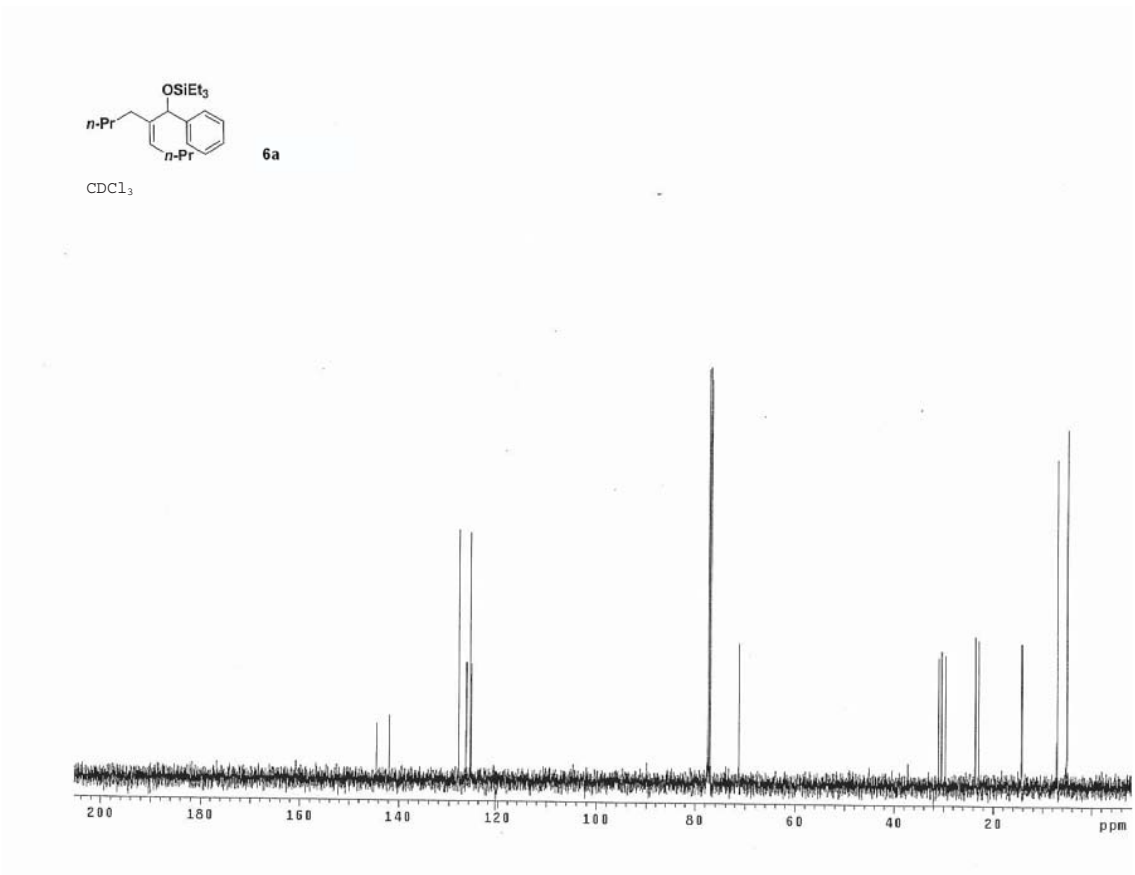
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 3.00 dB
SFO1 100.6228298 MHz

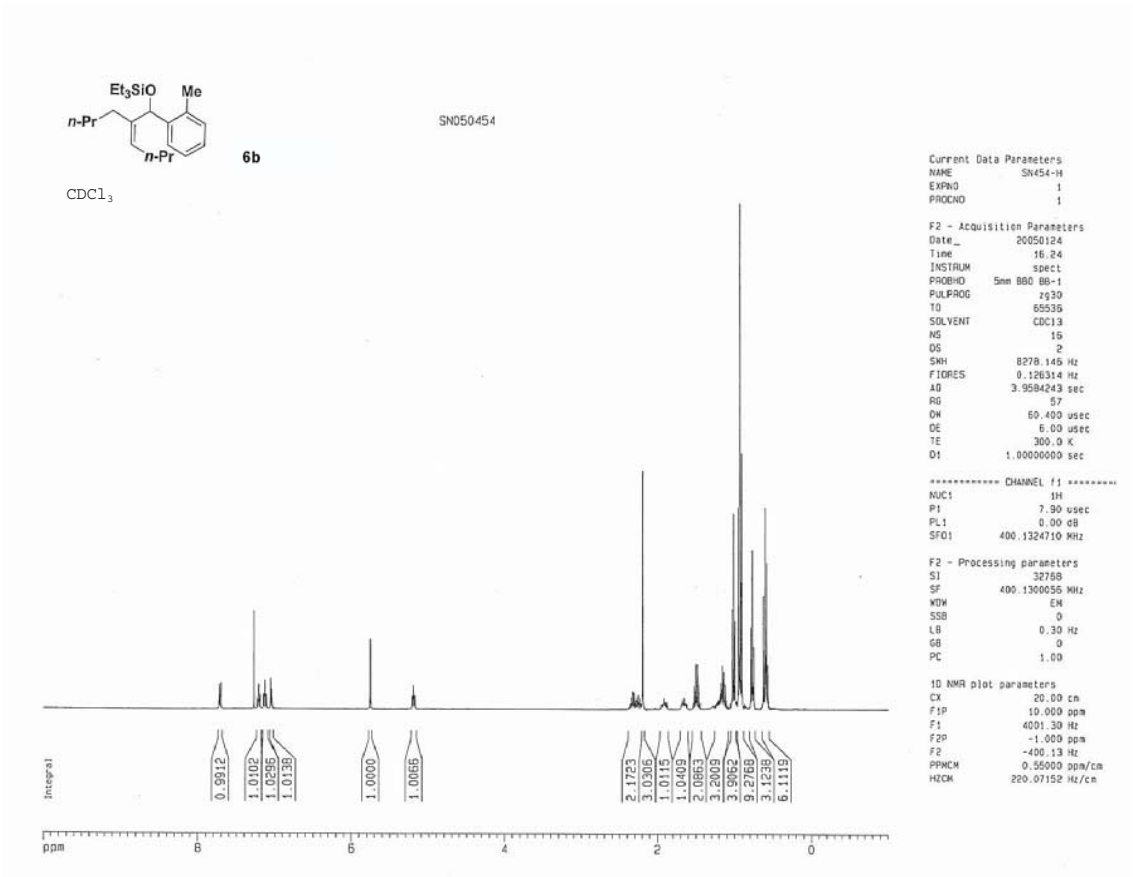
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 88.01 usec
PL2 3.00 dB
PL12 22.00 dB
PL13 22.00 dB
SFO2 400.1316005 MHz

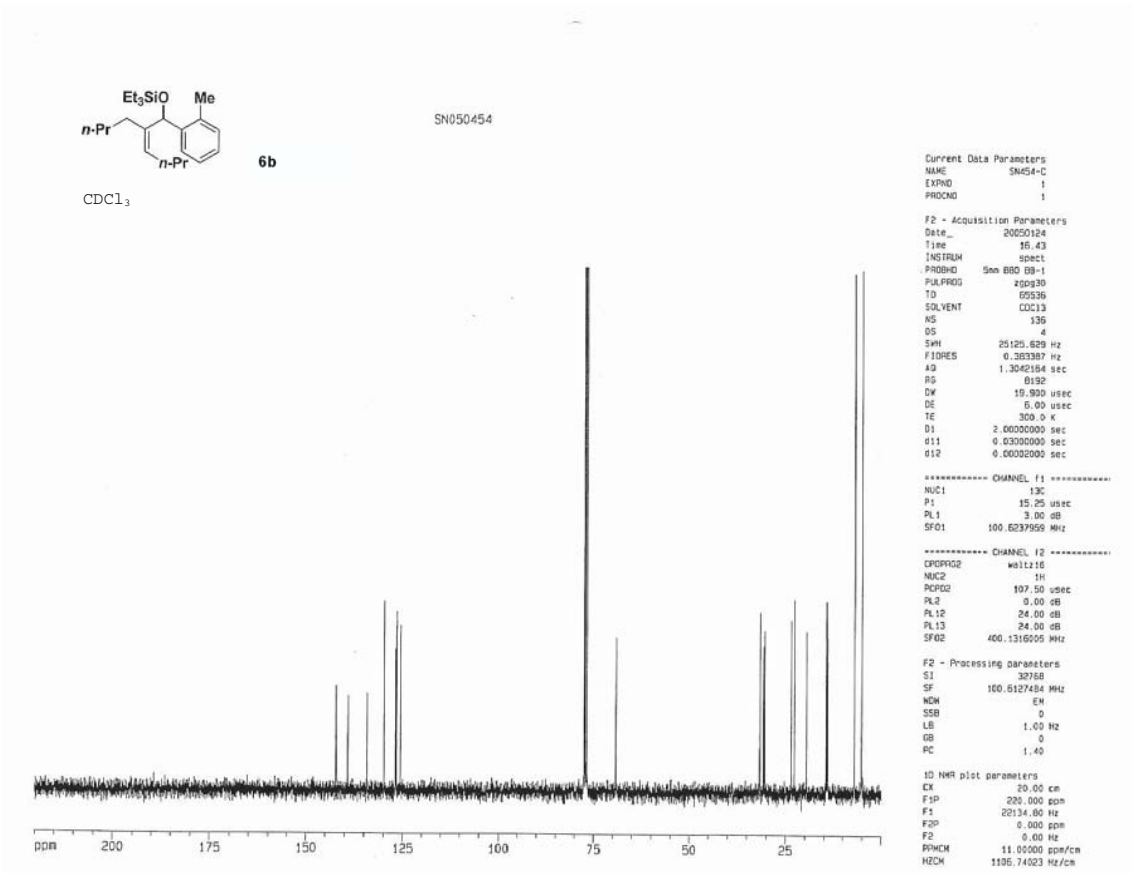
F2 - Processing parameters
SI 32768
SF 100.6127505 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

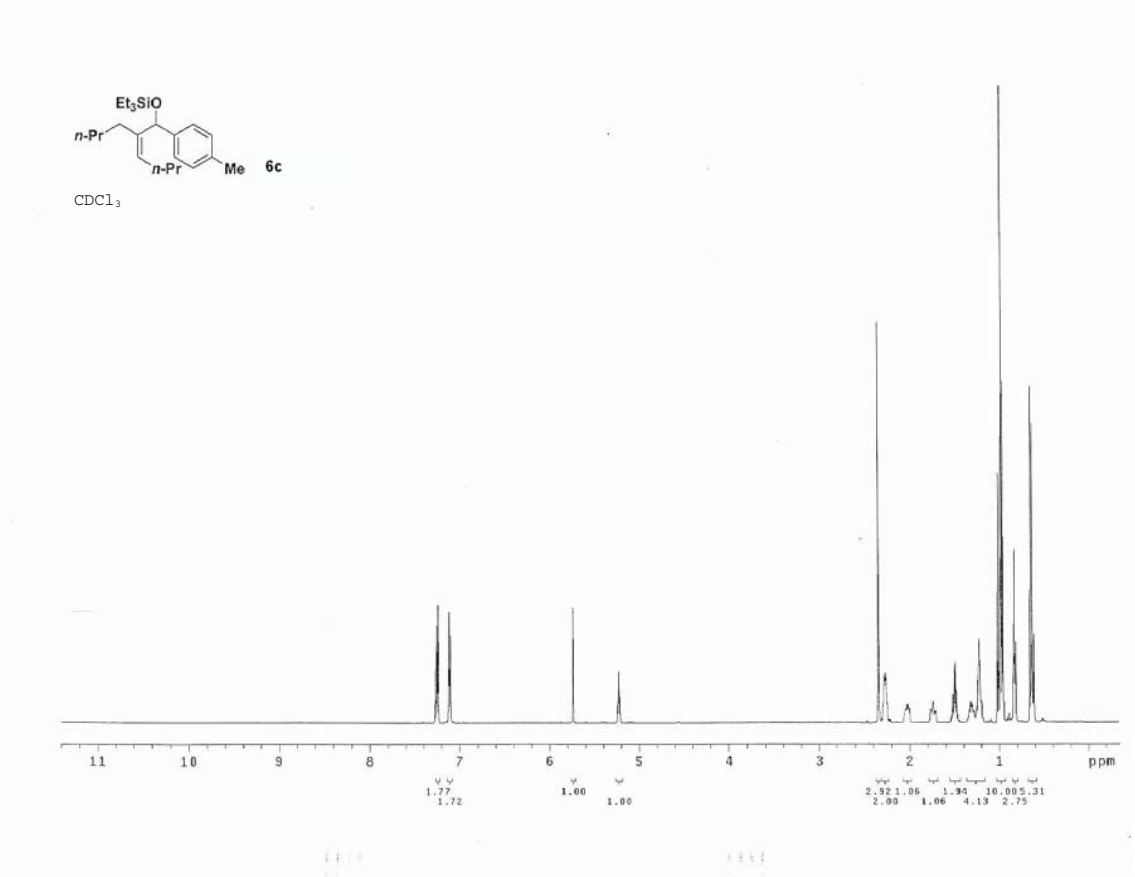
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 210.000 ppm
F1 21128.68 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.50000 ppm/cm
HZCM 1056.43384 Hz/cm

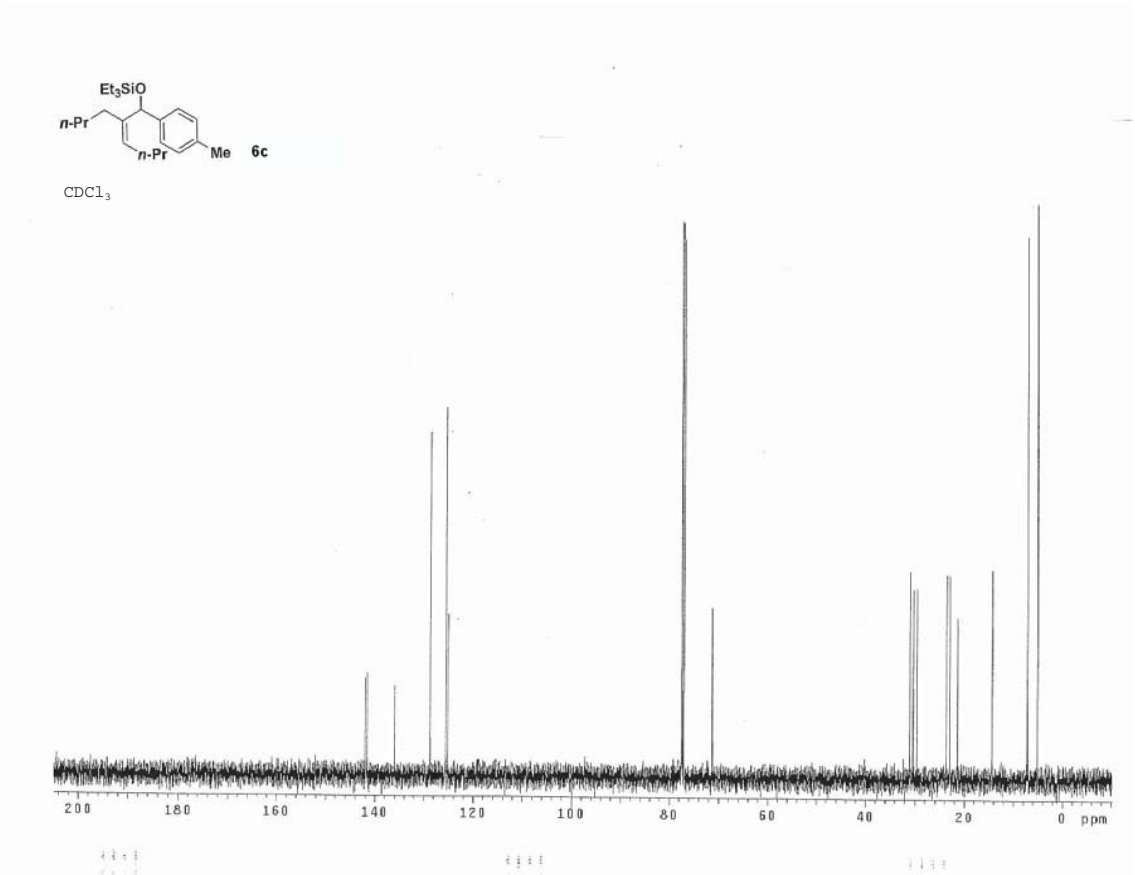

OSiEt3
n-Pr
n-Pr
6a
CDCl3
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.97
2.15
1.09
4.54
2.73

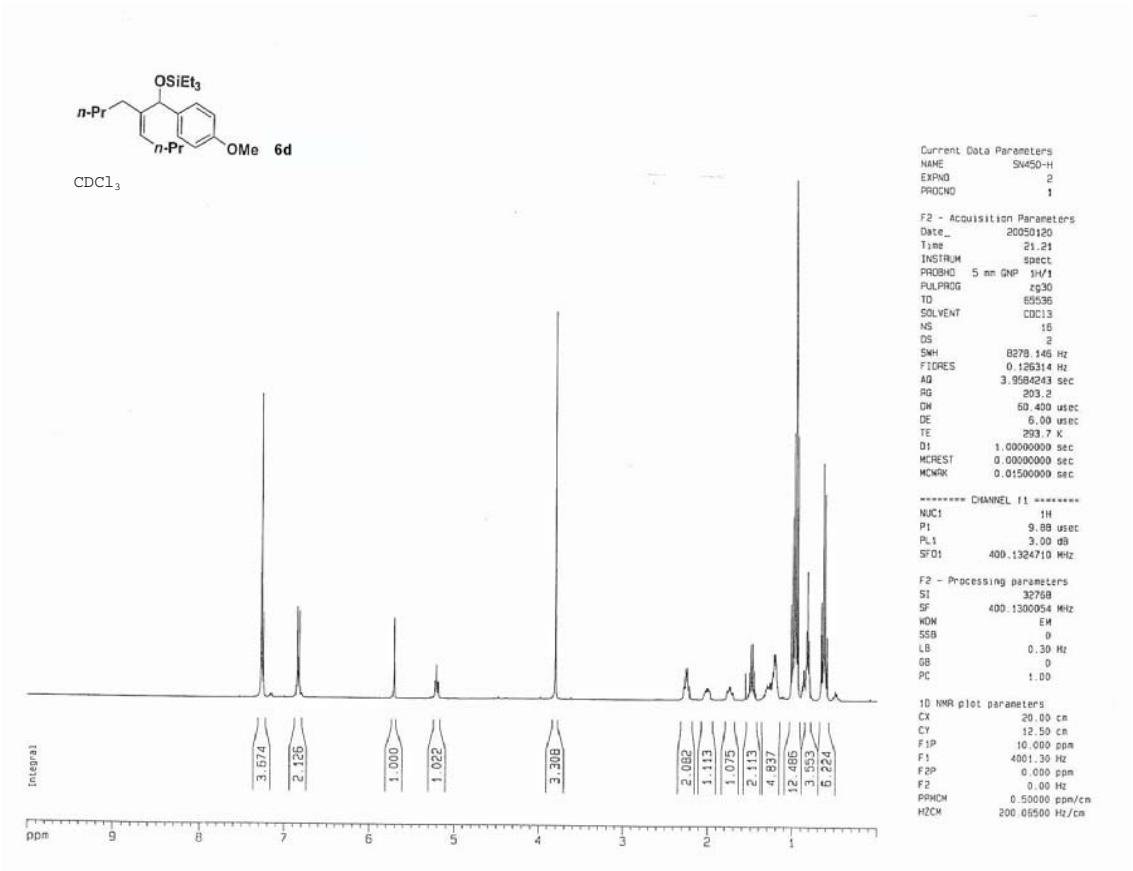

OSiEt3
n-Pr
n-Pr
6a
CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

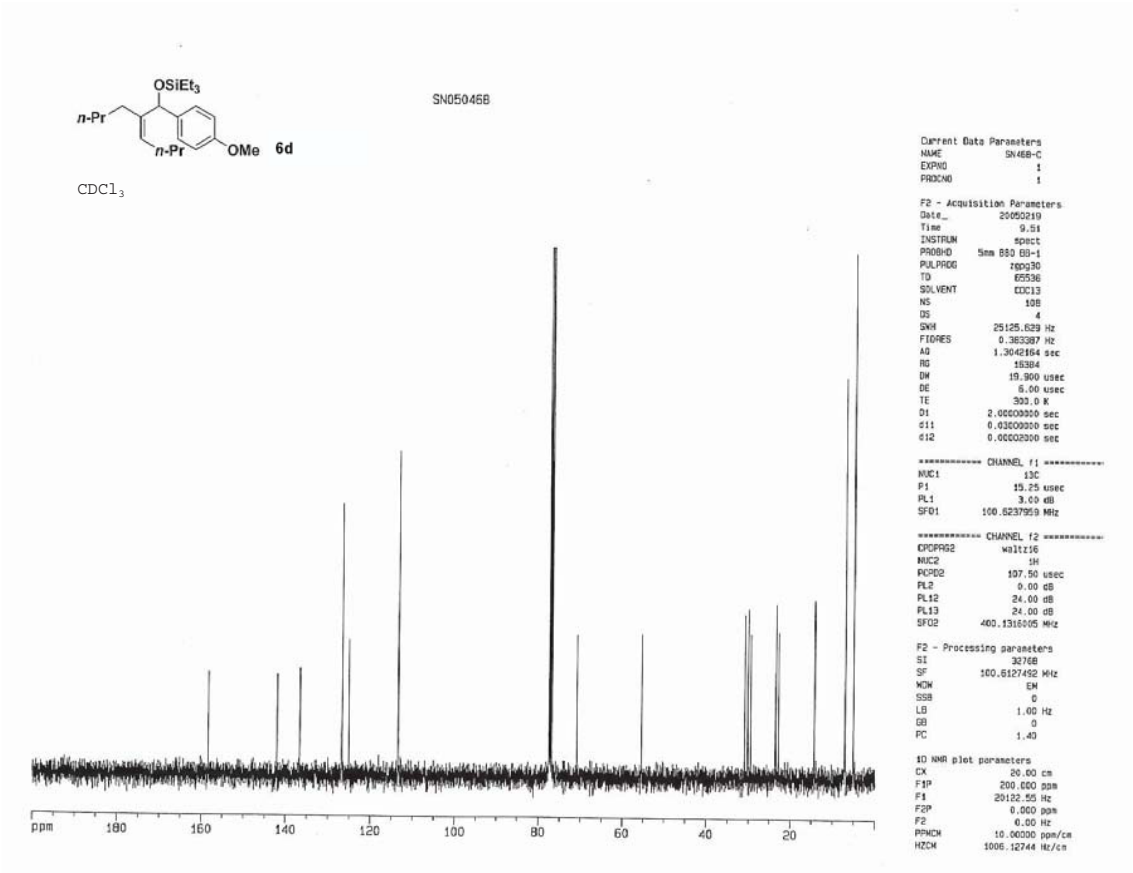

Et3SiO
Me
n-Pr
n-Pr
6b
SN050454
CDCl3
Current Data Parameters
NAME SN454-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050124
Time 16.24
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.145 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 57
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300056 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.55000 ppm/cm
HZCM 220.07152 Hz/cm
Integral
0.9912
1.0102
1.0295
1.0138
1.0000
1.0066
2.1723
3.0306
1.0115
1.0409
2.0863
3.2009
3.9962
9.2768
3.1238
6.1119
ppm
8
6
4
2
0

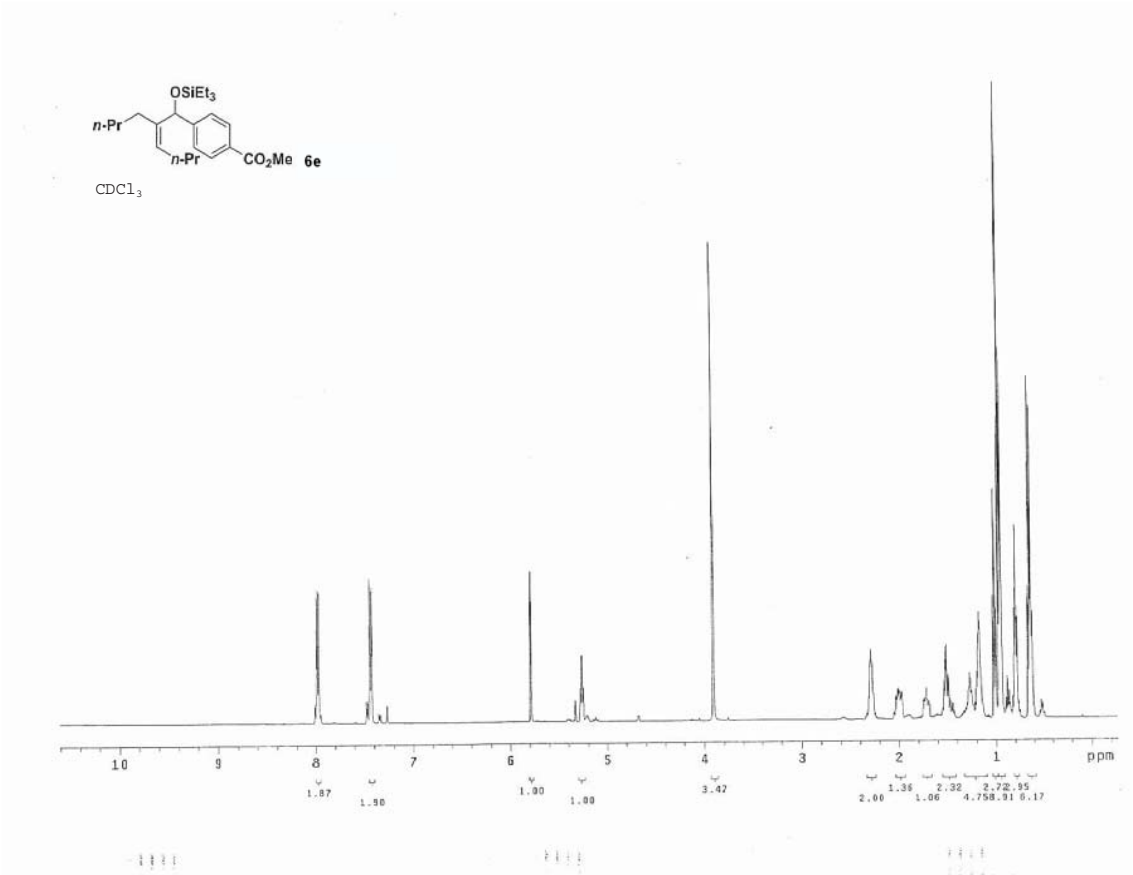

Et3SiO
Me
n-Pr
n-Pr
6b
SN050454
CDCl3
Current Data Parameters
NAME SN454-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050124
Time 16.43
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 136
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042184 sec
RG 8192
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127484 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 11.00000 ppm/cm
HZCM 1106.74023 Hz/cm
ppm
200
175
150
125
100
75
50
25

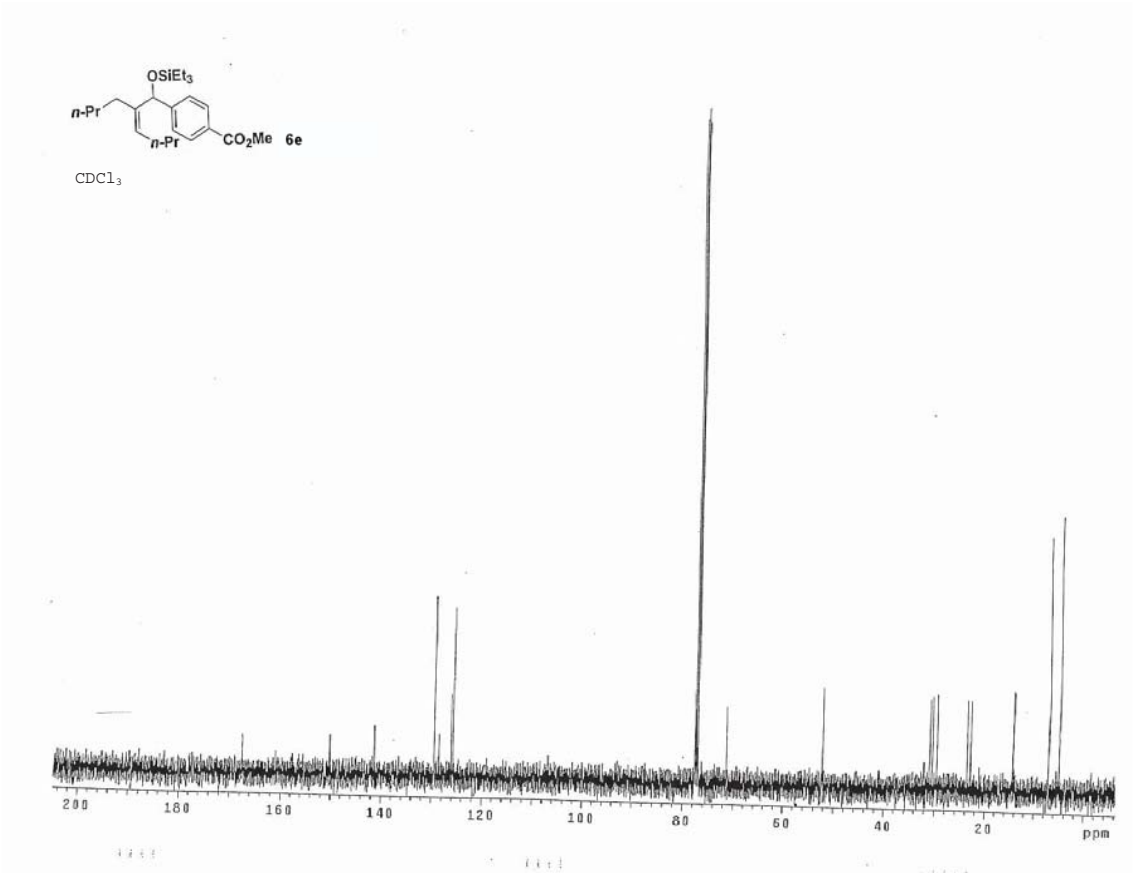

Et3SiO
n-Pr
n-Pr
Me
6c
CDCl3
11
10
9
8
7
6
5
4
3
2
1
ppm

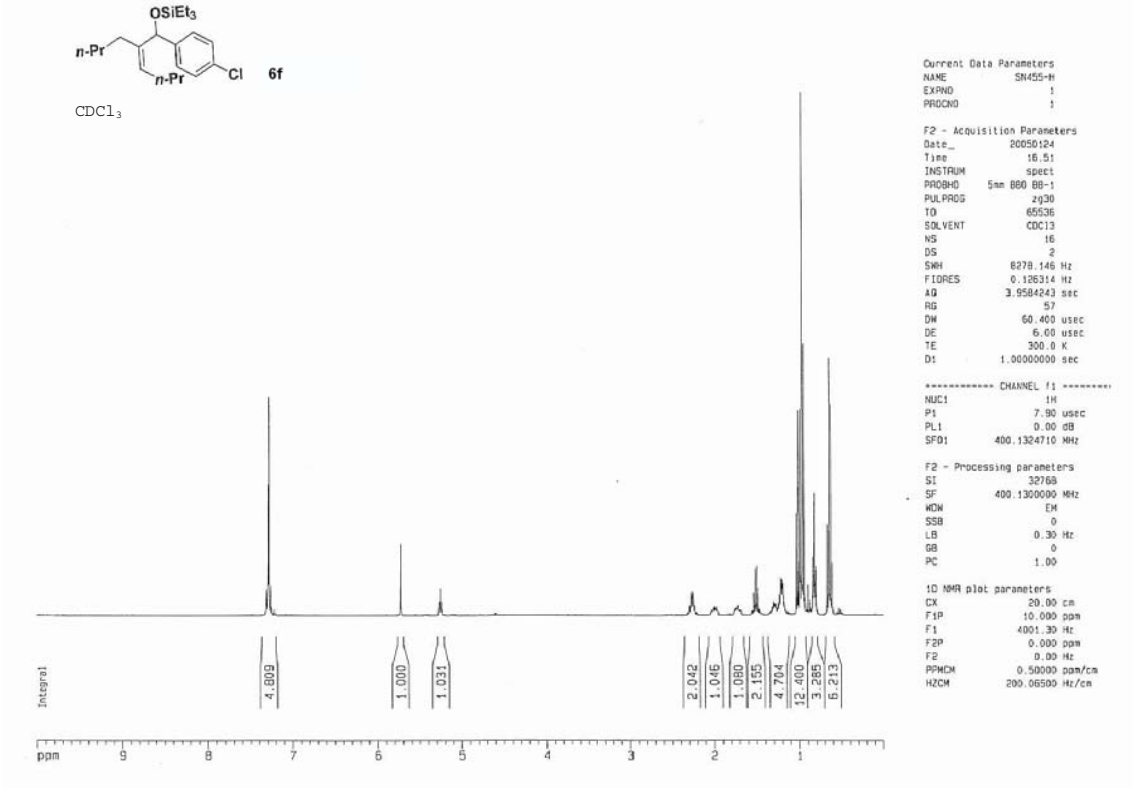

Et3SiO
n-Pr
n-Pr
Me
6c
CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm


OSiEt3
n-Pr
n-Pr
OMe
6d
CDCl3
Integral
3.674
2.126
1.000
1.022
3.308
2.082
1.113
1.075
2.113
4.837
12.486
3.553
6.224
ppm
Current Data Parameters
NAME SN450-H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050120
Time 21.21
INSTRUM spect
PROBHD 5 mm GNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 203.2
DW 60.400 usec
DE 6.00 usec
TE 293.7 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm


OSiEt3
n-Pr
n-Pr
OMe
6d
CDCl3
SN050468
ppm
Current Data Parameters
NAME SN468-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050219
Time 9.51
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 108
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042164 sec
RG 16384
DW 19.900 usec
DE 6.00 usec
TE 303.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
========== CHANNEL f1 ==========
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127492 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 200.000 ppm
F1 20122.55 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.00000 ppm/cm
HZCM 1006.12744 Hz/cm


OSiEt3
n-Pr
n-Pr
CO2Me 6e
CDCl3
10
9
8
7
6
5
4
3
2
1
ppm
1.87
1.98
1.90
1.00
3.42
2.00
1.36
1.06
2.32
2.72
2.95
4.75
8.91
6.17


OSiEt3
n-Pr
n-Pr
CO2Me 6e
CDCl3
200
180
160
140
120
100
80
60
40
20
ppm


OSiEt3
n-Pr
n-Pr
Cl
6f
CDCl3
Integral
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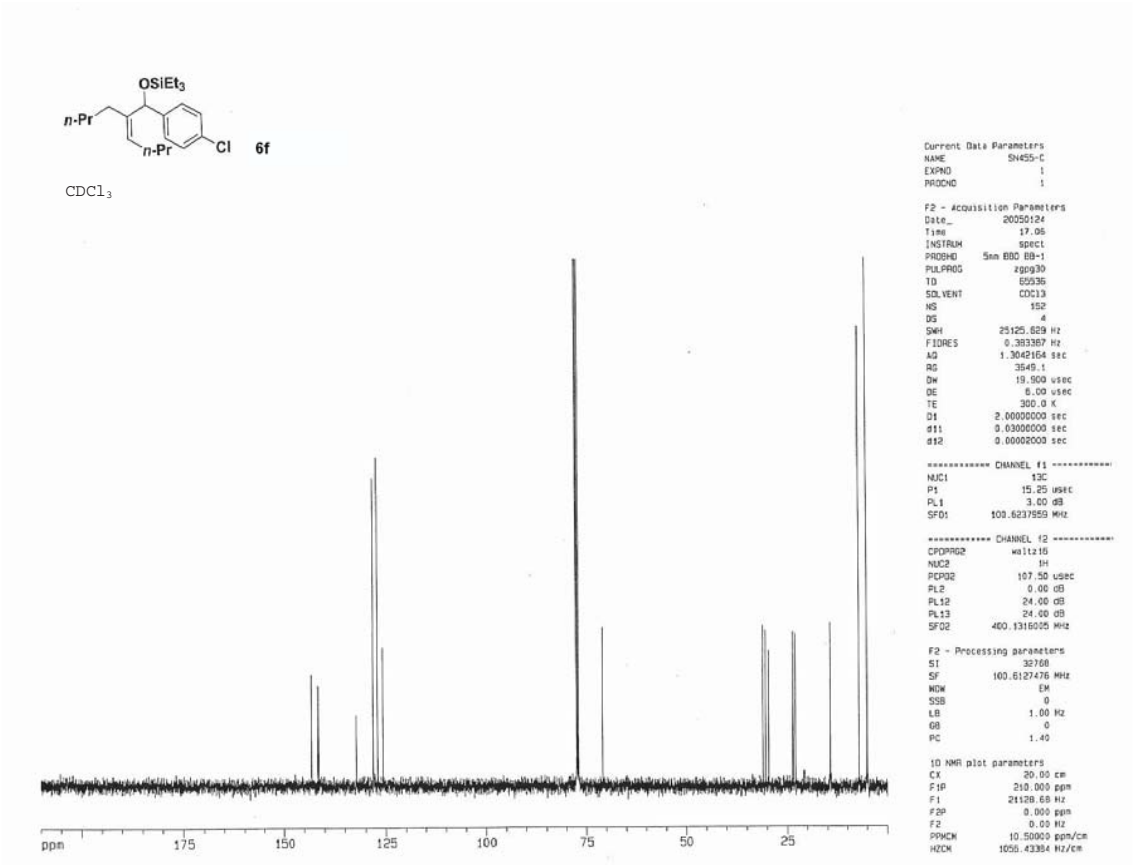
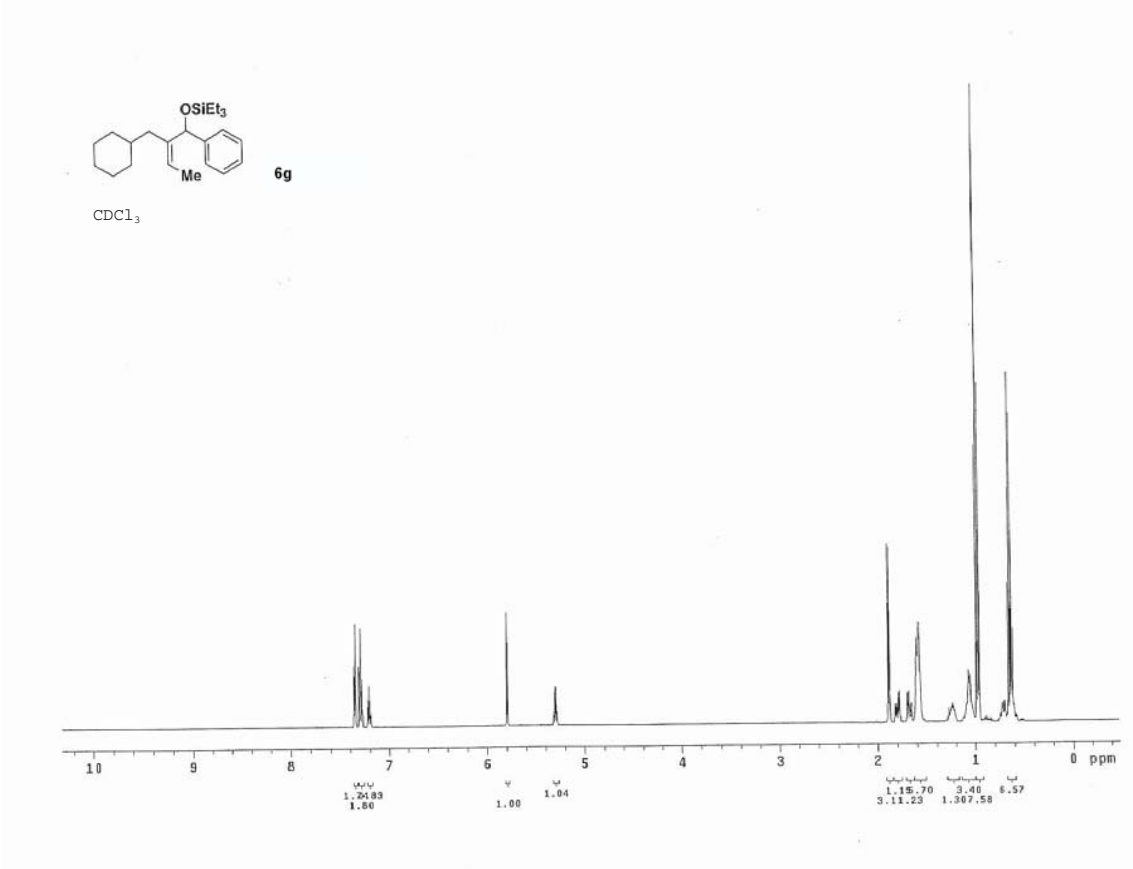
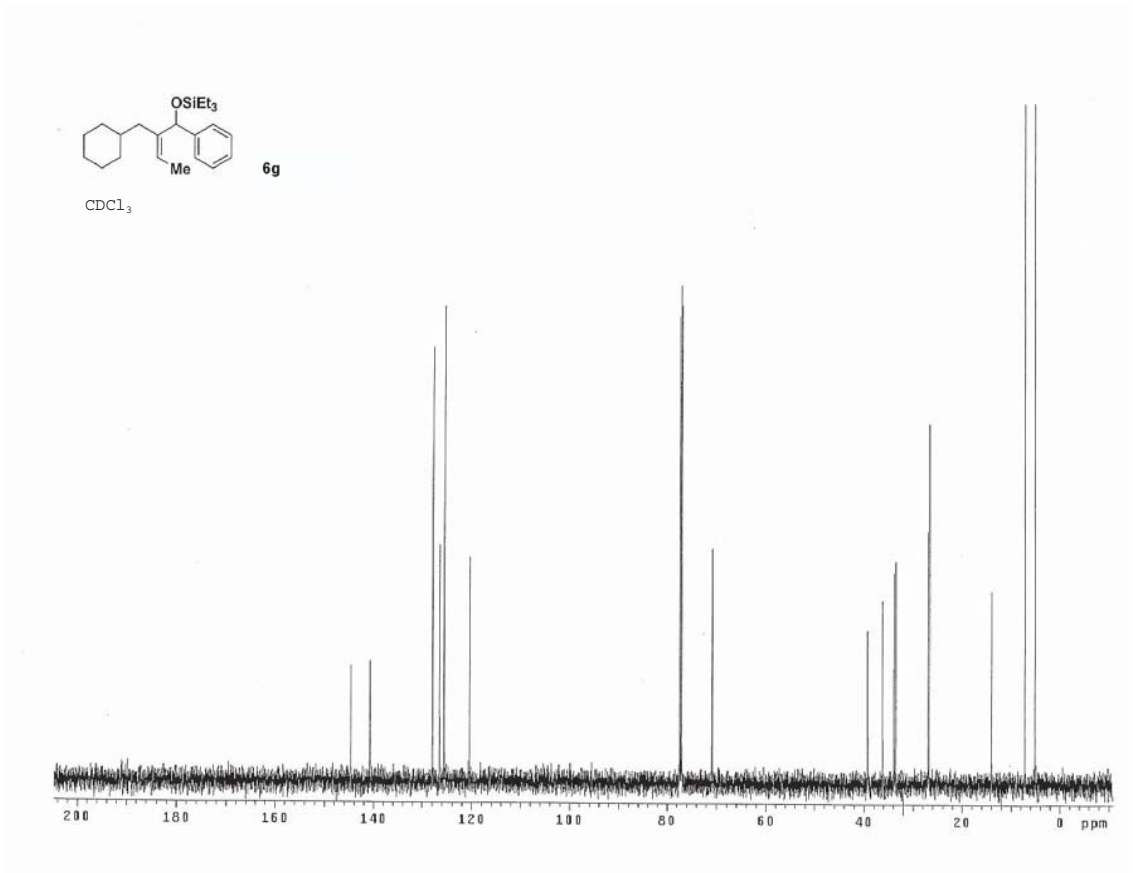
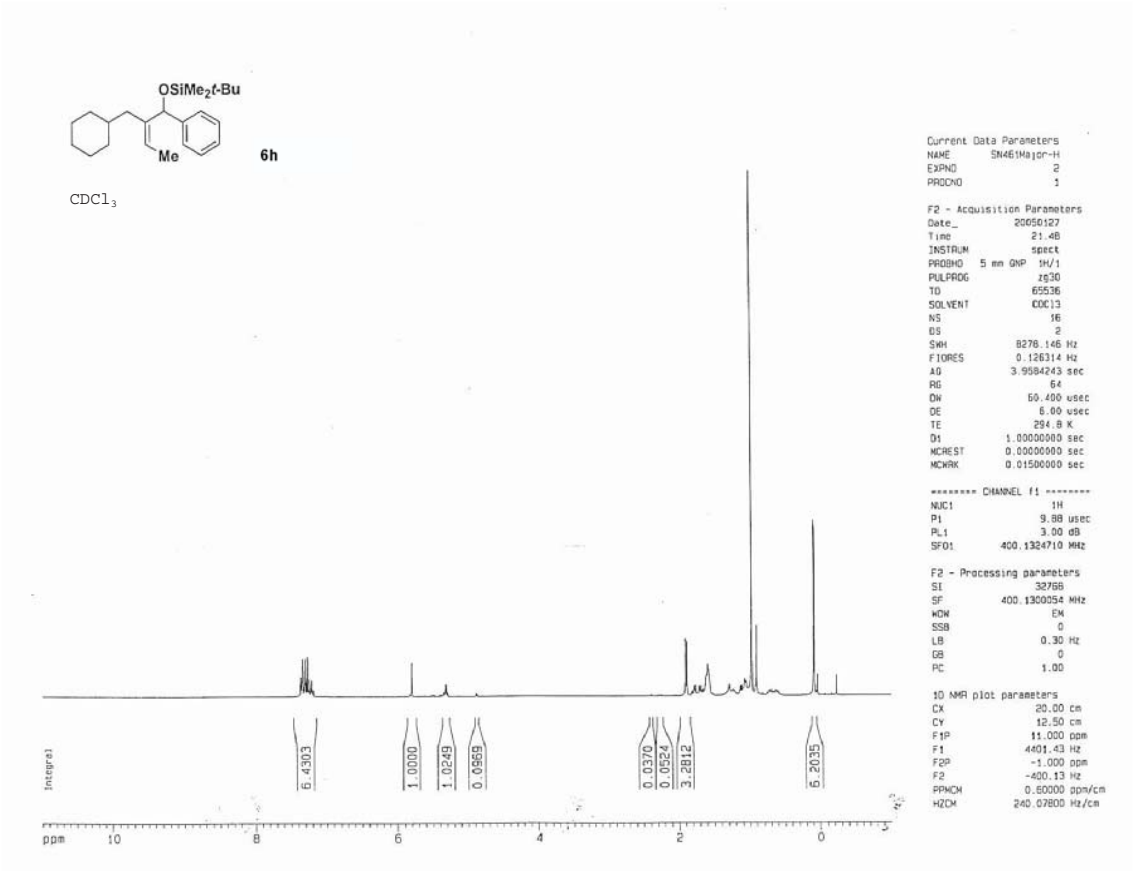
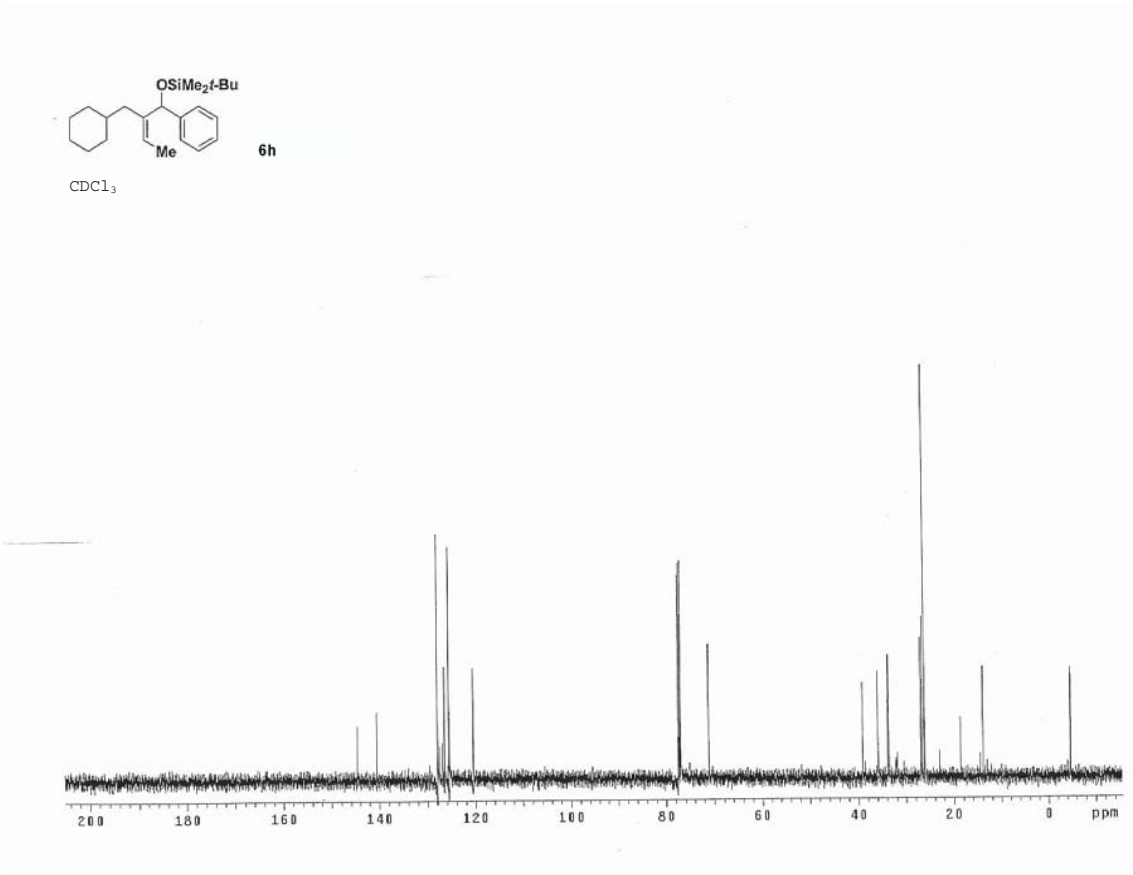
1.000
1.031
2.042
1.046
1.080
2.155
4.704
12.400
3.285
6.213
ppm
9
8
7
6
5
4
3
2
1
Current Data Parameters
NAME SN455-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050124
Time 16.51
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 57
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm

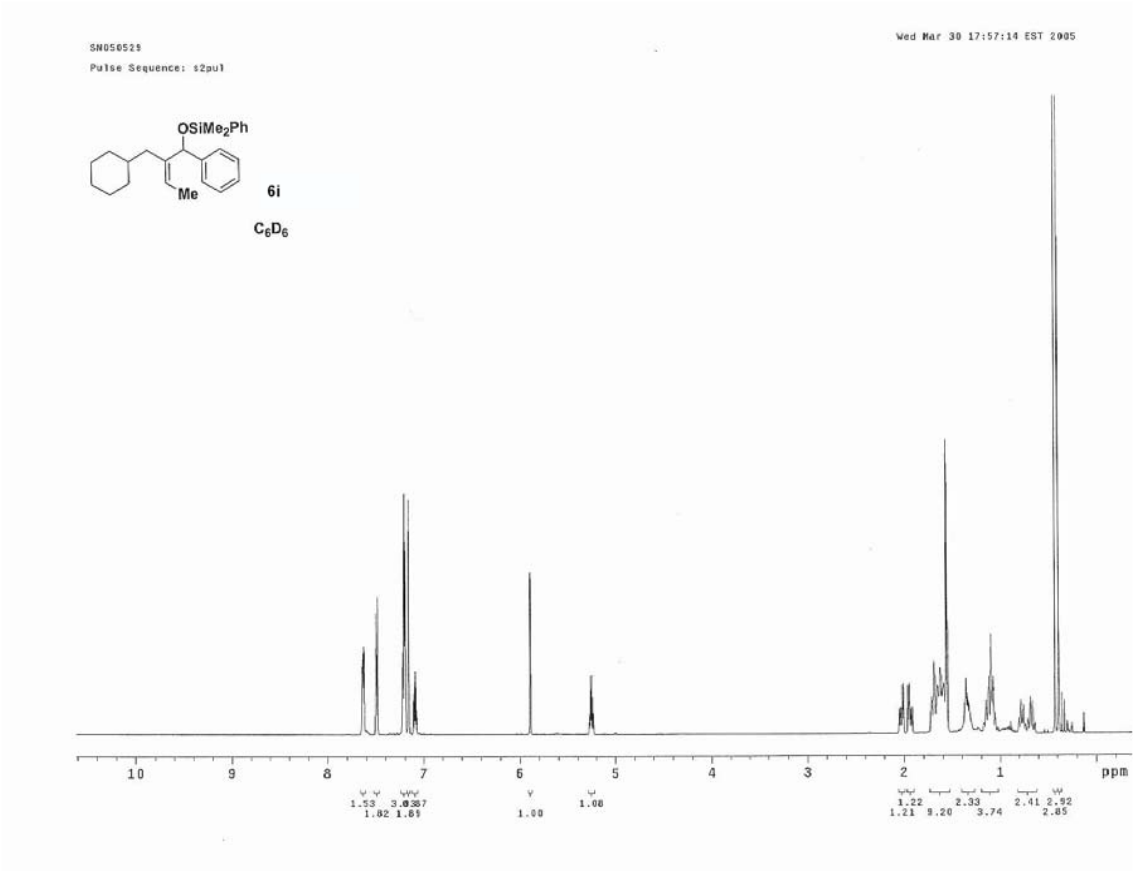

OSiEt3
n-Pr
n-Pr
Cl
6f
CDCl3
ppm
175
150
125
100
75
50
25
Current Data Parameters
NAME SN455-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050124
Time 17.06
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 152
DS 4
SWH 25125.629 Hz
FIDRES 0.383367 Hz
AQ 1.3042164 sec
RG 3549.1
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237559 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127476 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 210.000 ppm
F1 21128.68 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.50000 ppm/cm
HZCM 1056.43384 Hz/cm

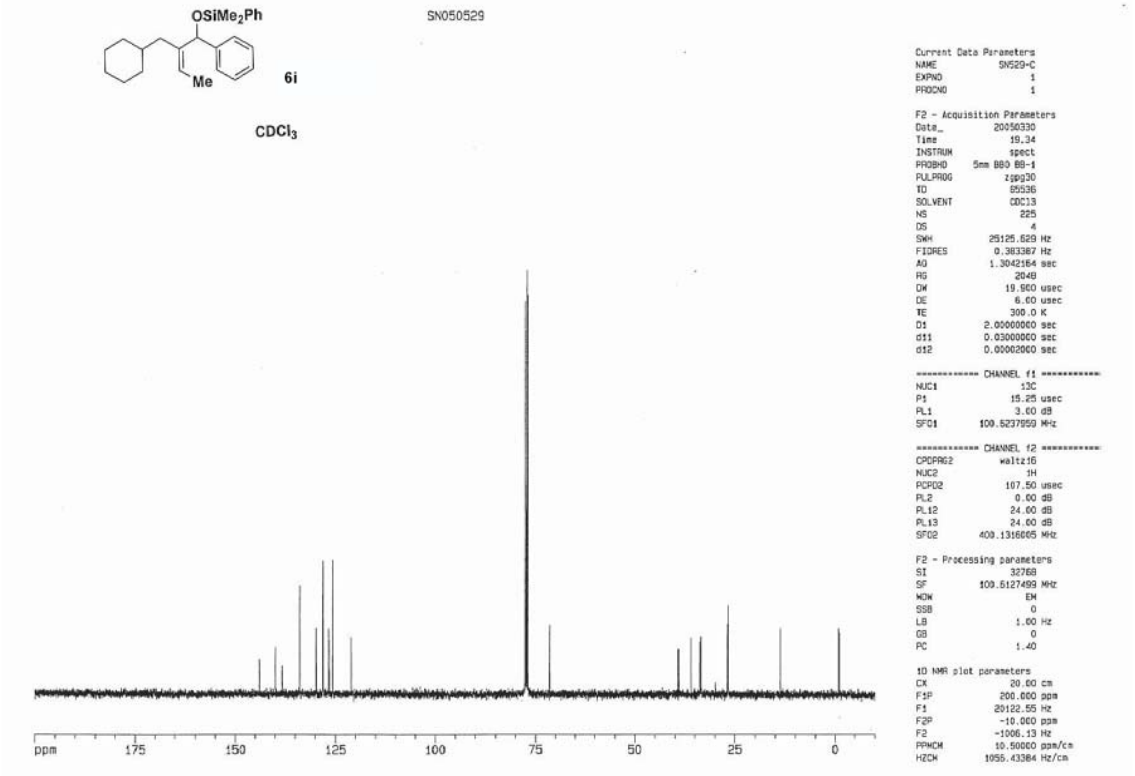

OSiEt3
Me
6g
CDCl3
10
9
8
7
6
5
4
3
2
1
0 ppm
1.24
1.83
1.80
1.00
1.04
1.15
5.70
3.11.23
3.40
1.307.58
6.57


OSiEt3
Me
6g
CDCl3
200
180
160
140
120
100
80
60
40
20
0 ppm


OSiMe2t-Bu
Me
6h
CDCl3
Current Data Parameters
NAME SN461Major-H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050127
Time 21.48
INSTRUM spect
PROBHD 5 mm GNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 64
DW 60.400 usec
DE 6.00 usec
TE 294.8 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 11.000 ppm
F1 4401.43 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 240.07800 Hz/cm
Integral
6.4303
1.0000
1.0249
0.0959
0.0370
0.0524
3.2812
5.2035
ppm
10
8
6
4
2
0


OSiMe2t-Bu
Me
6h
CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm


SN050529
Pulse Sequence: s2pul
Wed Mar 30 17:57:14 EST 2005
OSiMe2Ph
Me
6i
C6D6
10
9
8
7
6
5
4
3
2
1
ppm
1.53
3.0387
1.82
1.89
1.00
1.08
1.22
2.33
2.41
2.92
1.21
9.20
3.74
2.85


OSiMe2Ph
Me
6i
CDCl3
SN050529
ppm
175
150
125
100
75
50
25
0
Current Data Parameters
NAME SN529-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050330
Time 19.34
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 225
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042164 sec
RG 2048
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.5237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127499 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
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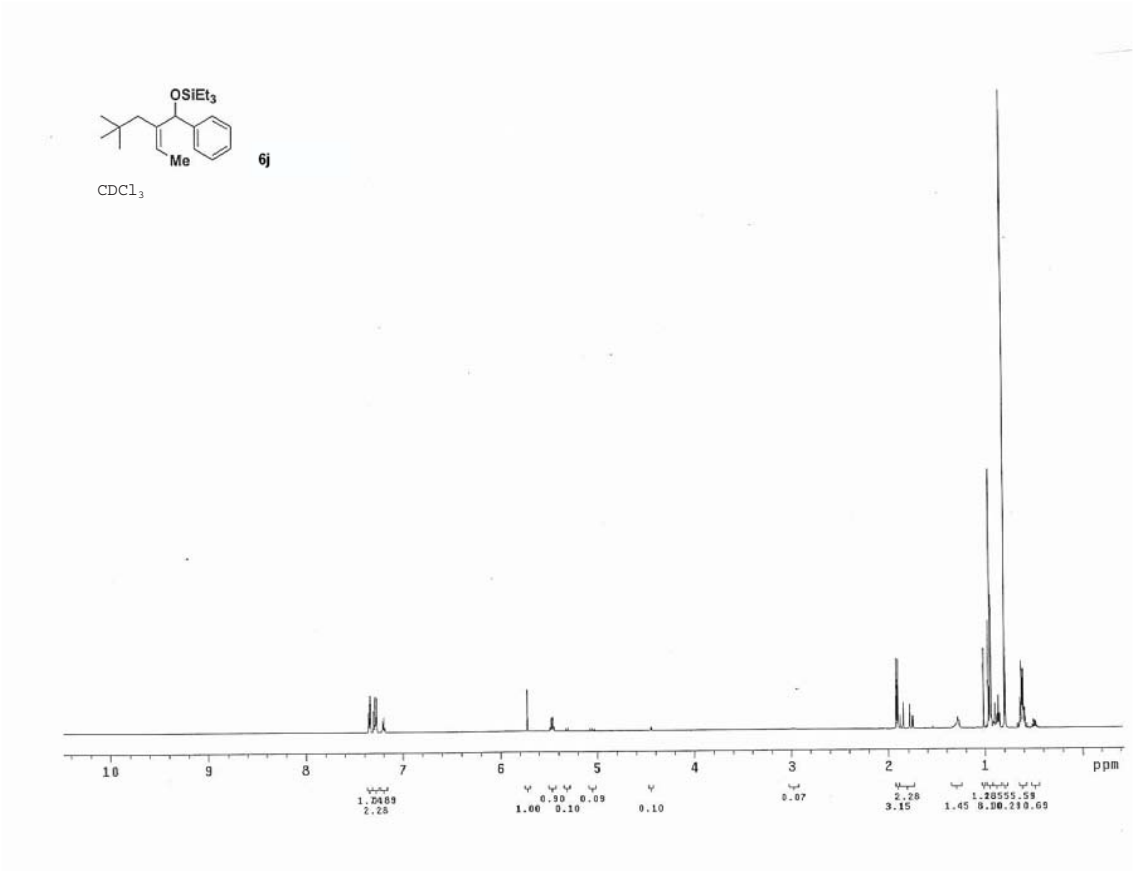
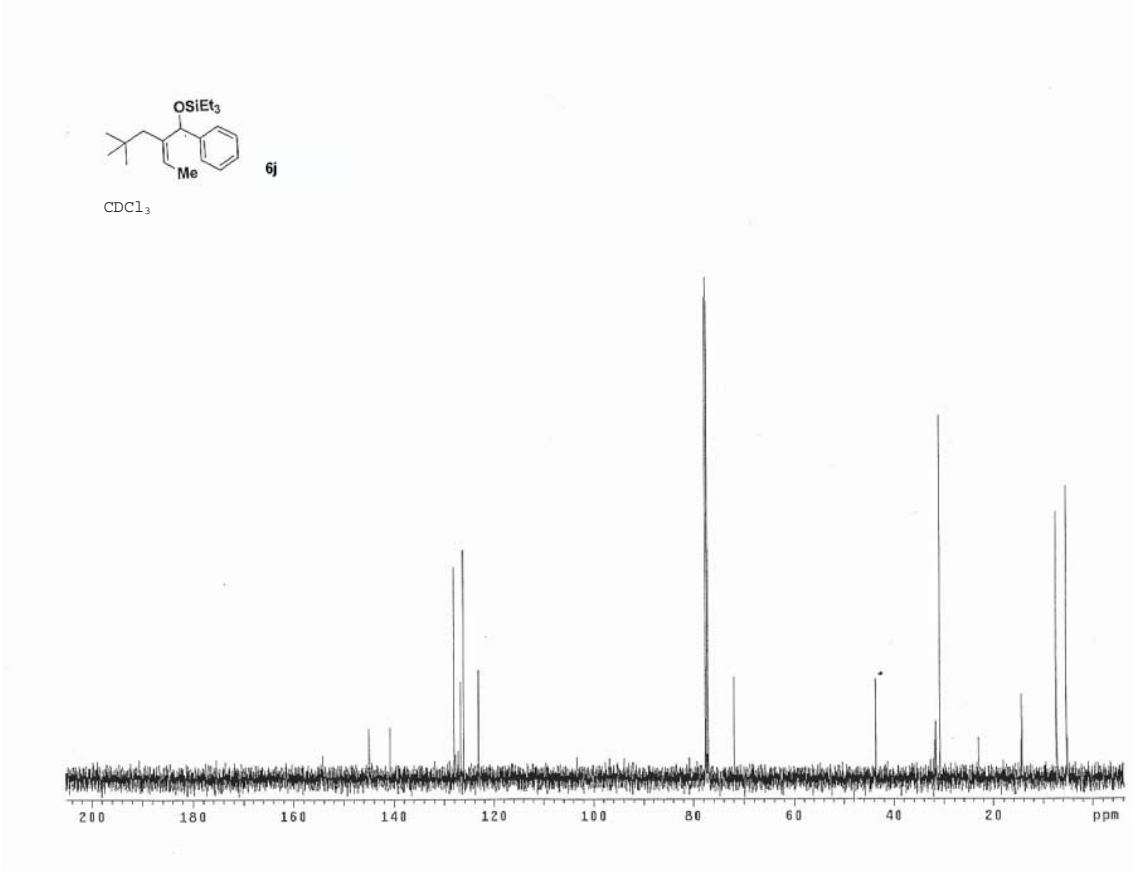
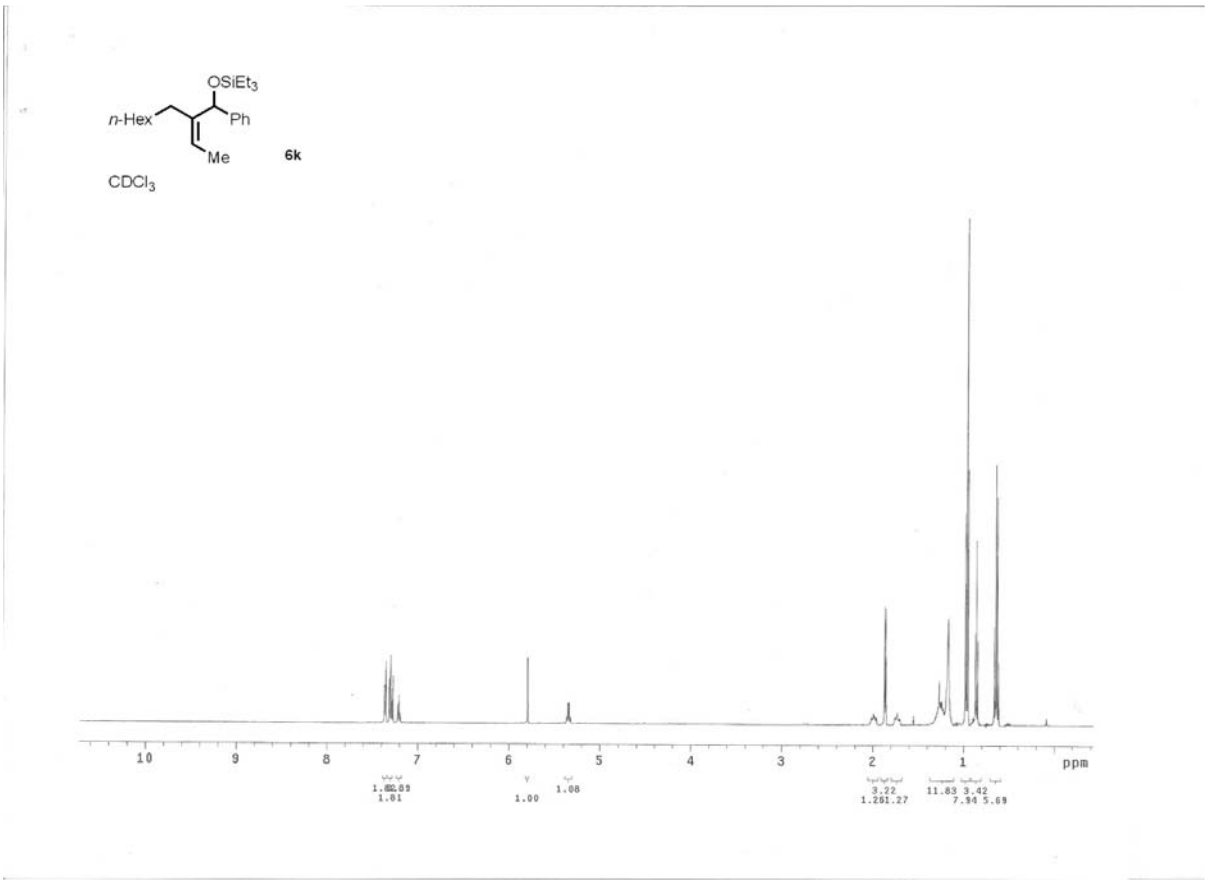
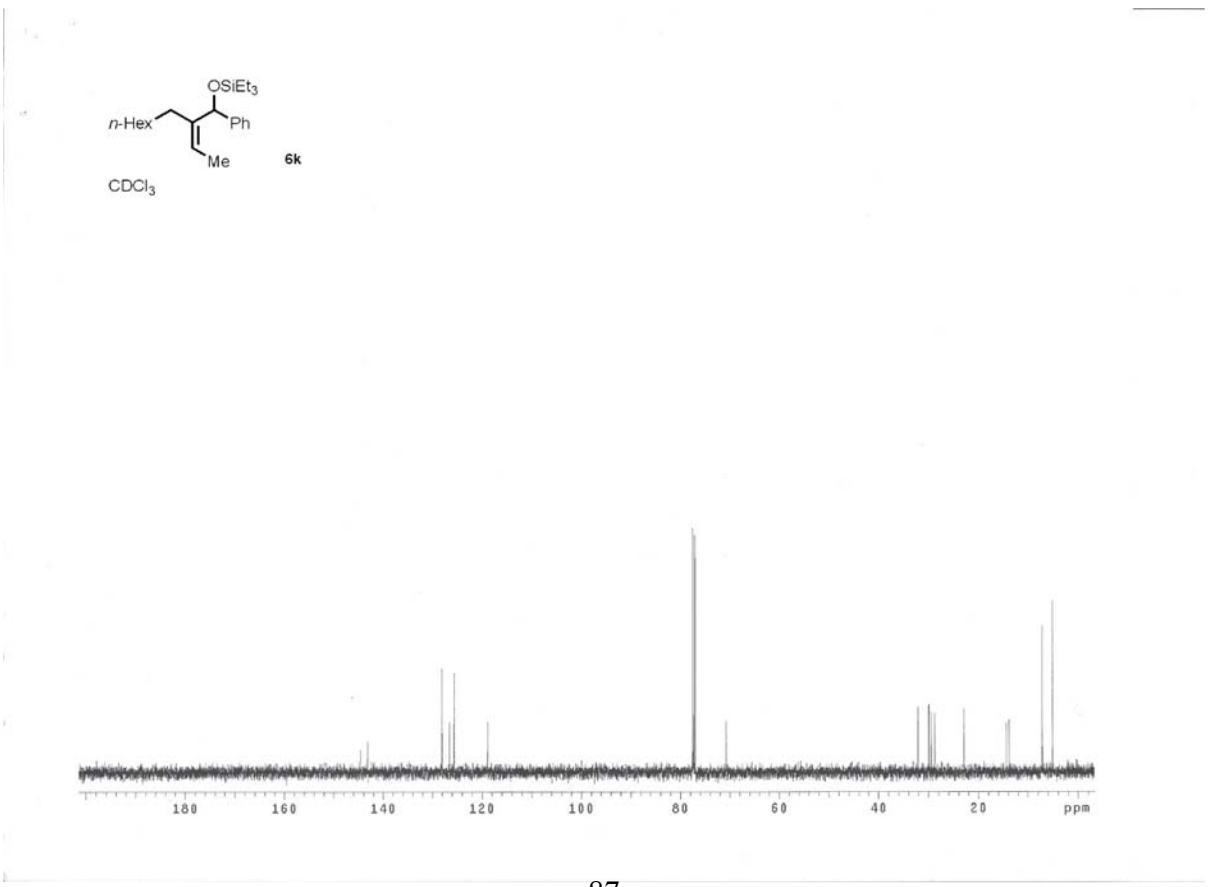
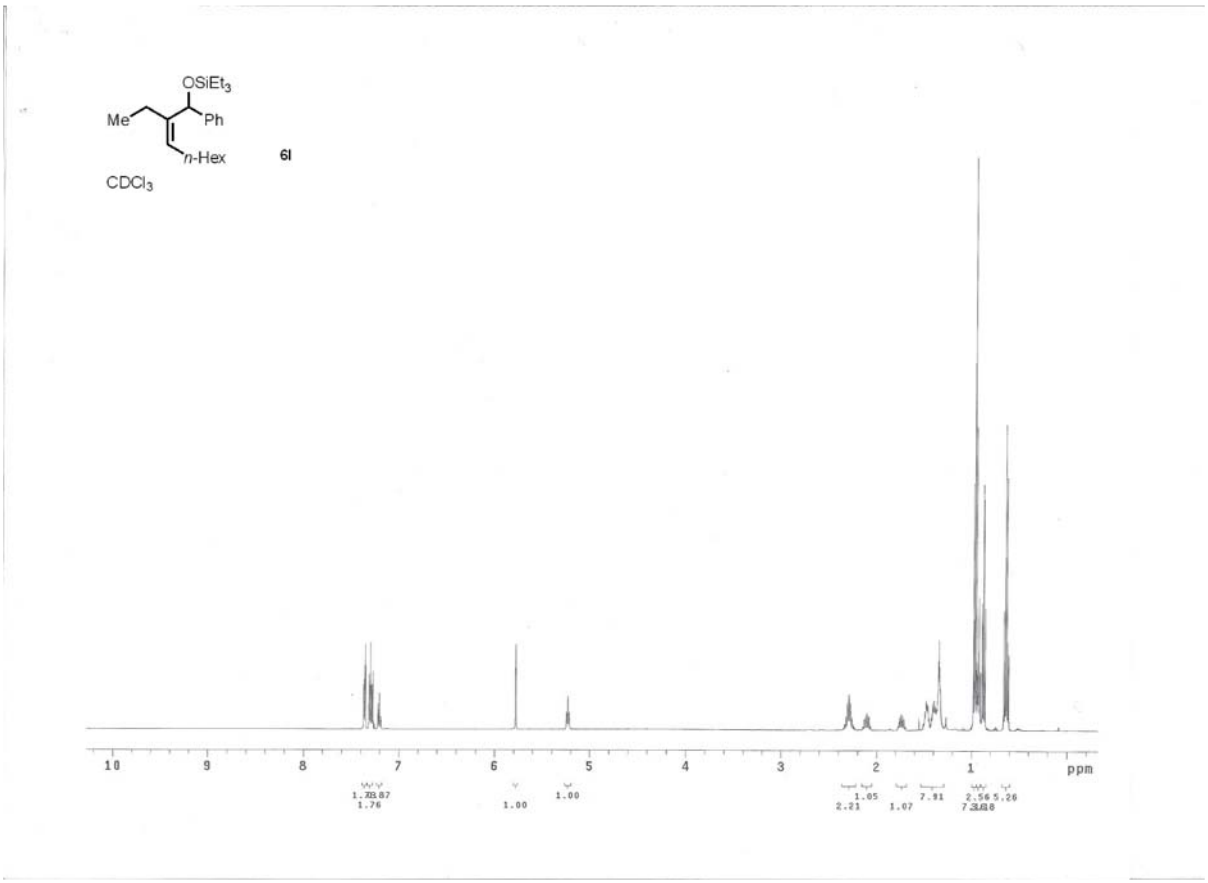
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 10.50000 ppm/cm
HZCM 1055.43384 Hz/cm

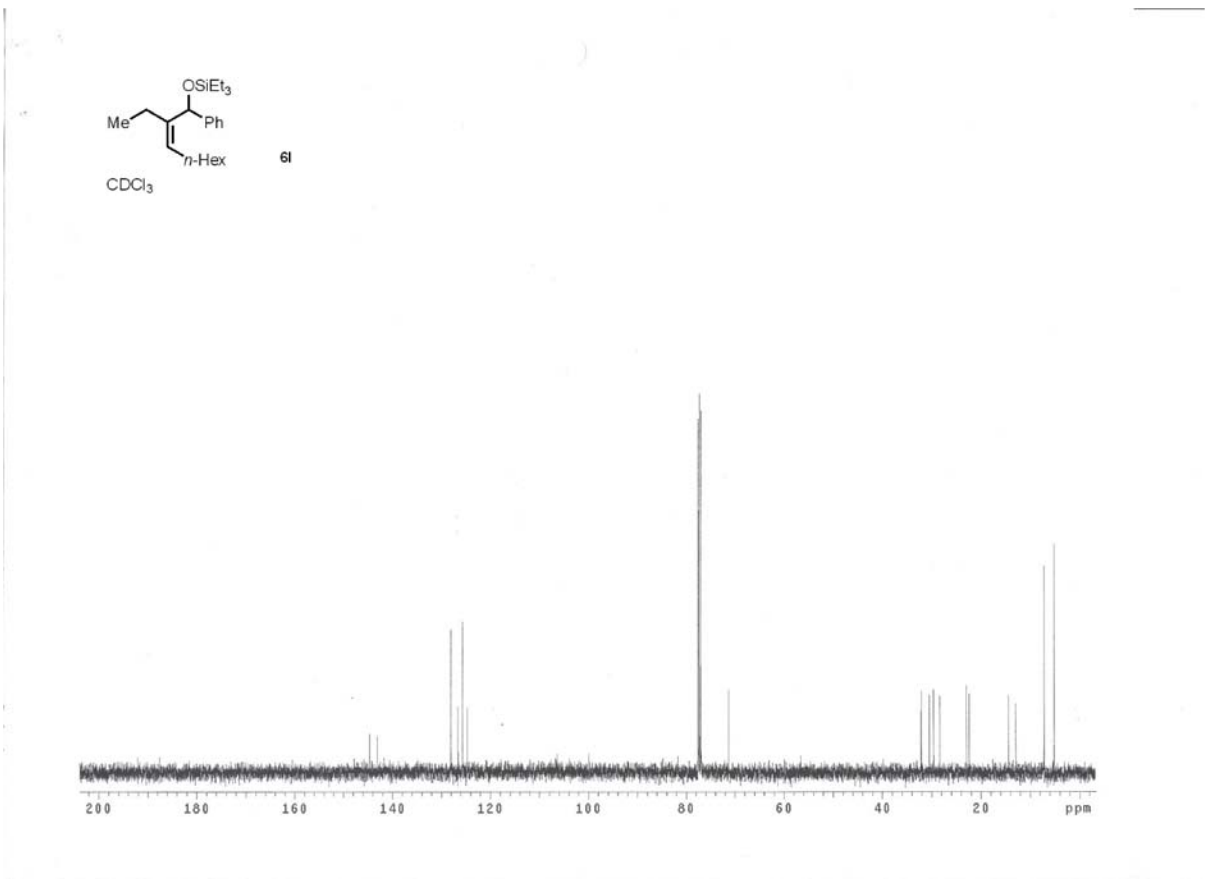

OSiEt3
Me
6j
CDCl3
10
9
8
7
6
5
4
3
2
1
ppm

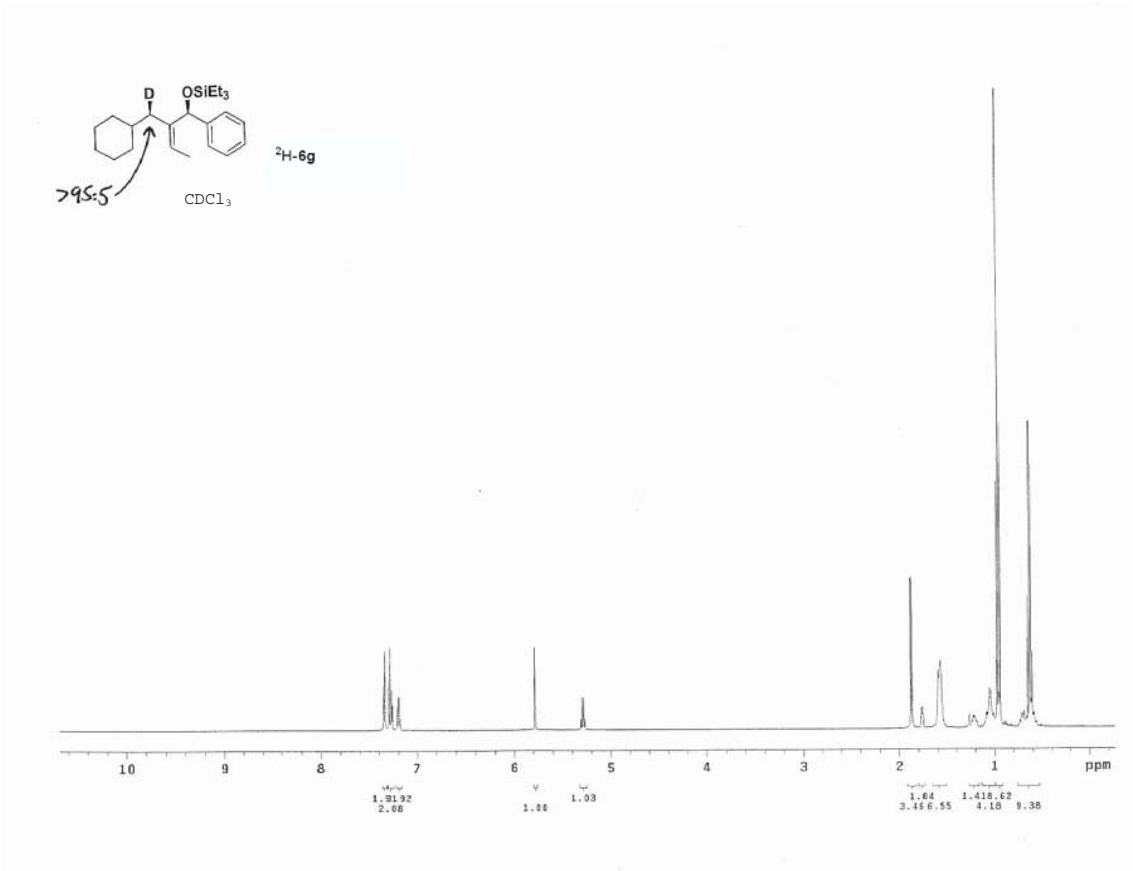

OSiEt3
Me
6j
CDCl3
200
180
160
140
120
100
80
60
40
20
ppm

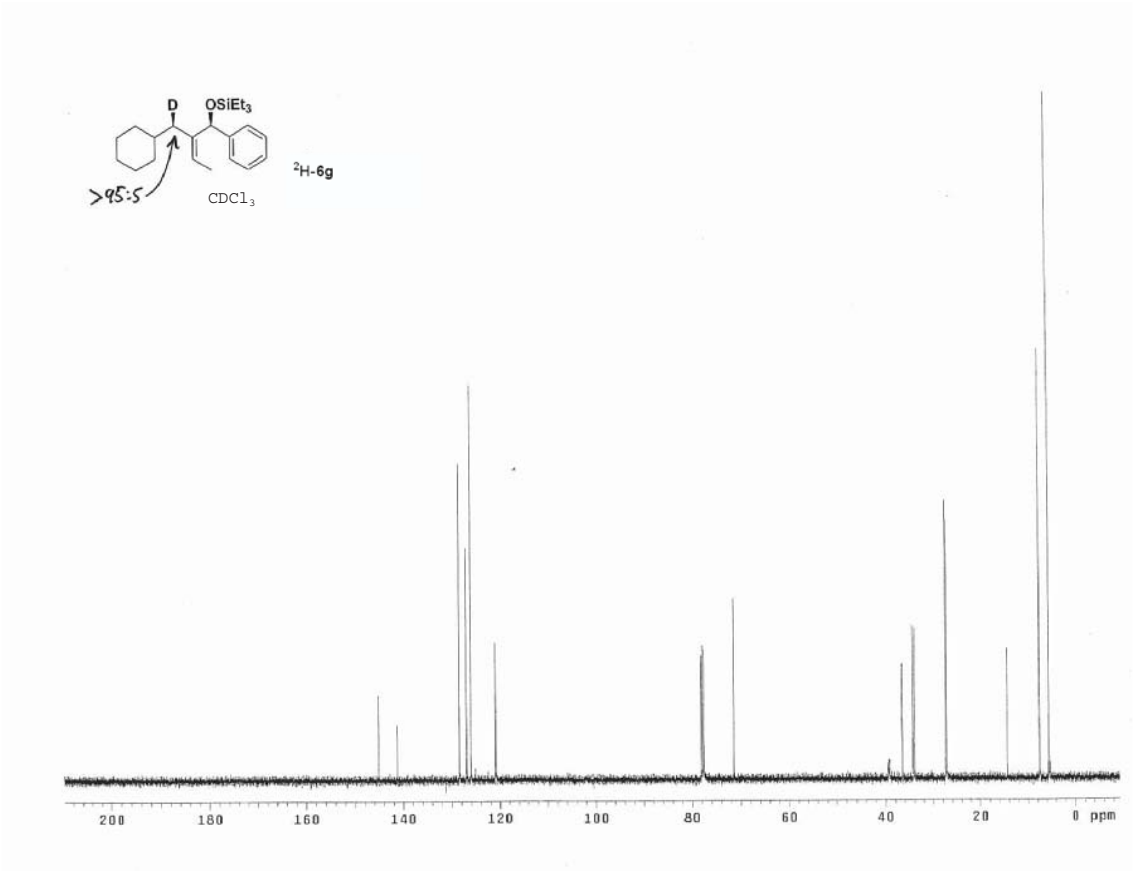

OSiEt3
n-Hex
Ph
Me
6k
CDCl3
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
3.22
1.26
1.27
11.83
3.42
7.94
5.69

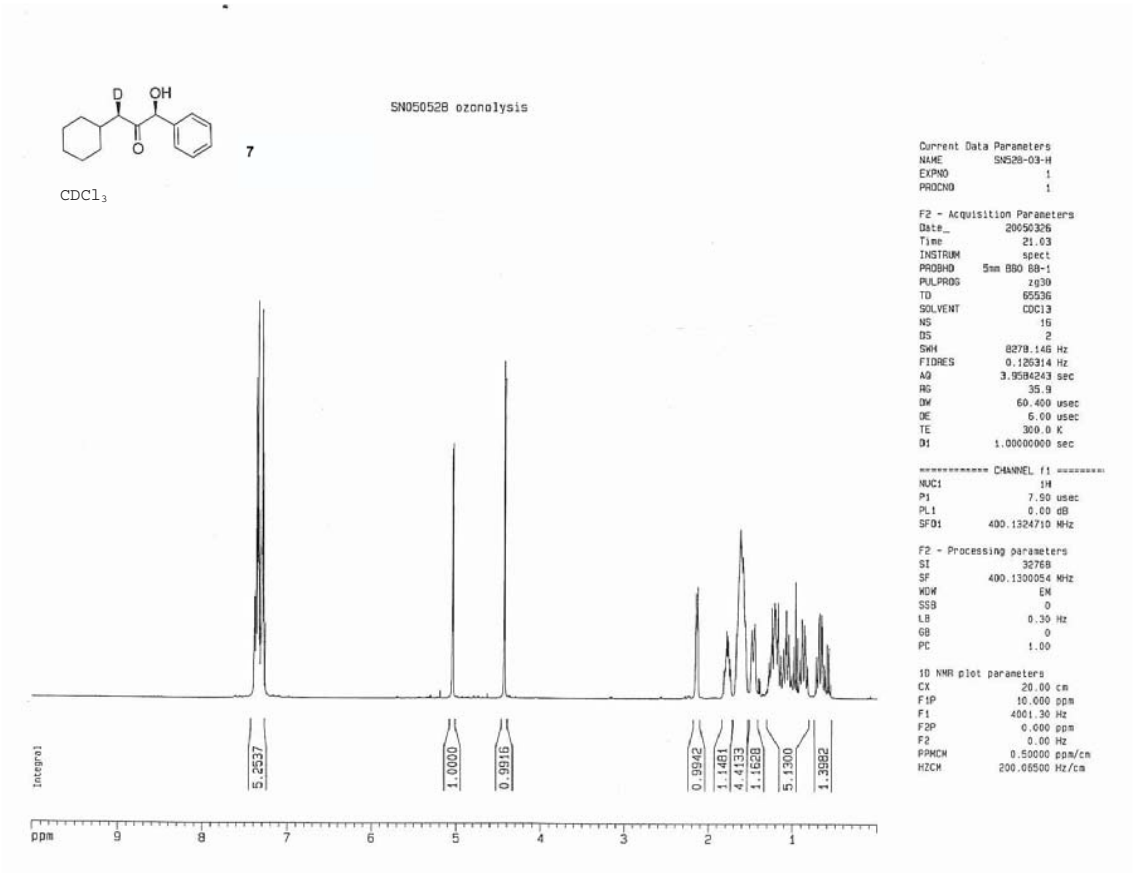

OSiEt3
n-Hex
Ph
Me
6k
CDCl3
180
160
140
120
100
80
60
40
20
ppm

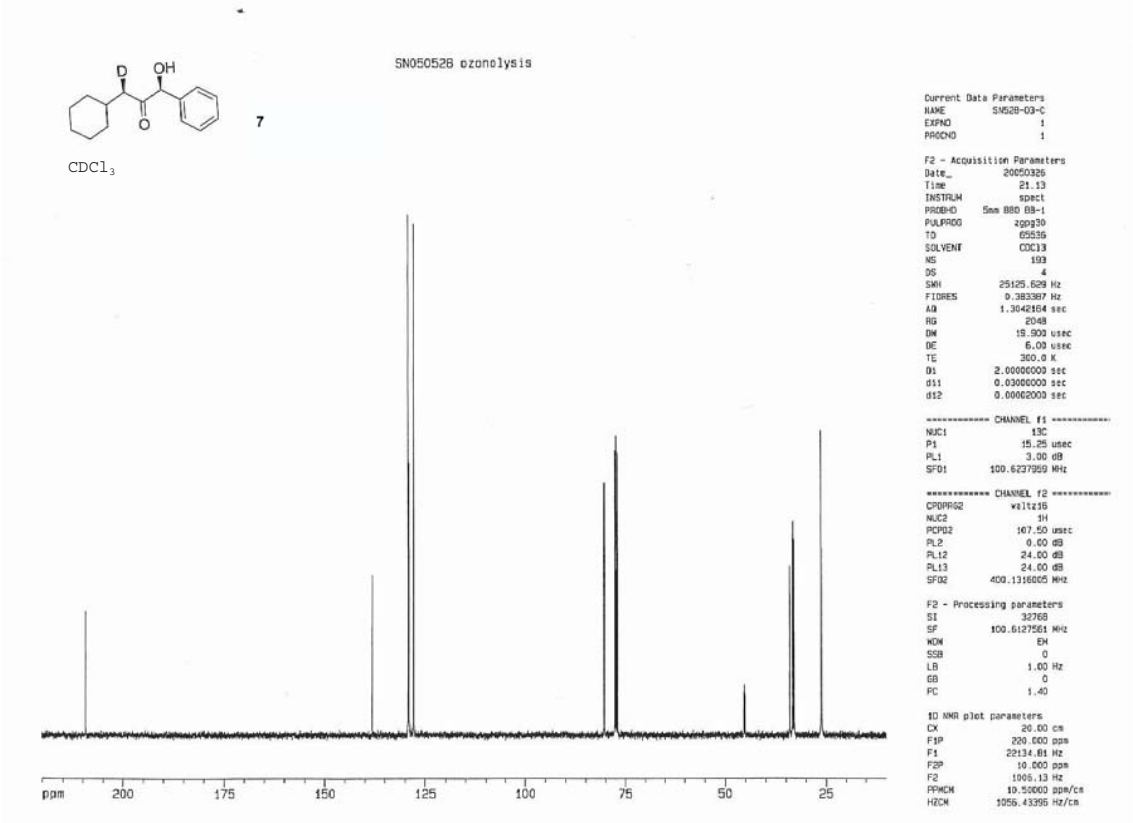

OSiEt3
Me
Ph
n-Hex
CDCl3
6l
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.05
2.21
1.07
7.91
2.56
5.26

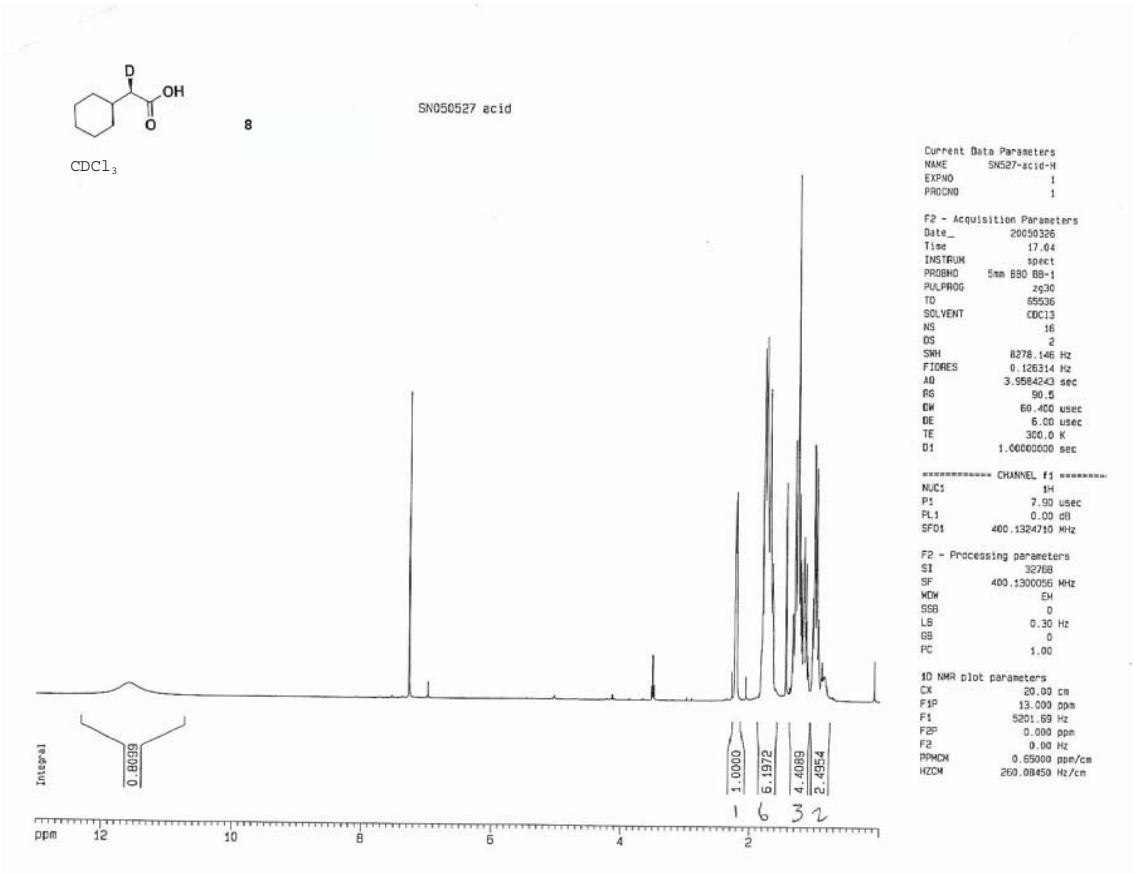

OSiEt3
Me
Ph
n-Hex
CDCl3
6l
200
180
160
140
120
100
80
60
40
20
ppm

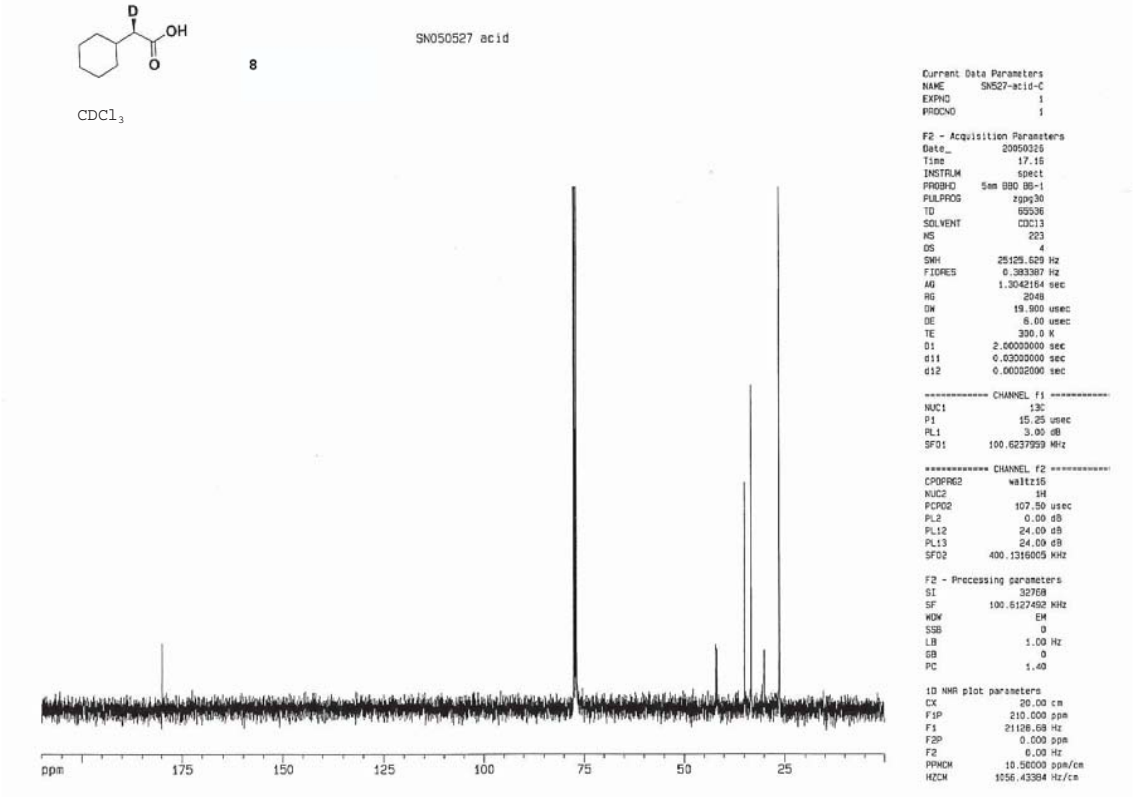

D
OSiEt3
>95:5
CDCl3
2H-6g
10
9
8
7
6
5
4
3
2
1
ppm
1.91 92
2.08
1.00
1.03
1.64
3.45 6.55
1.41 8.62
4.18
9.38

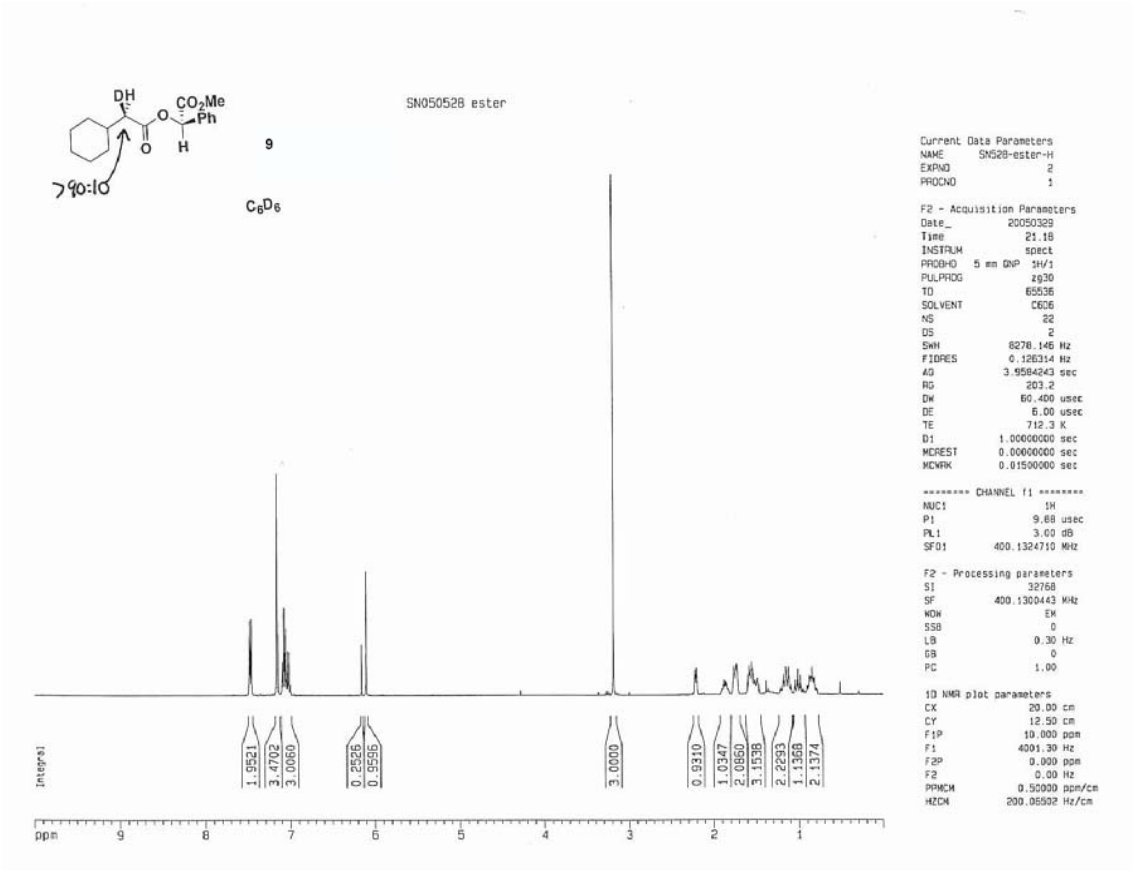

D
OSiEt3
>95:5
CDCl3
2H-6g
200
180
160
140
120
100
80
60
40
20
0 ppm

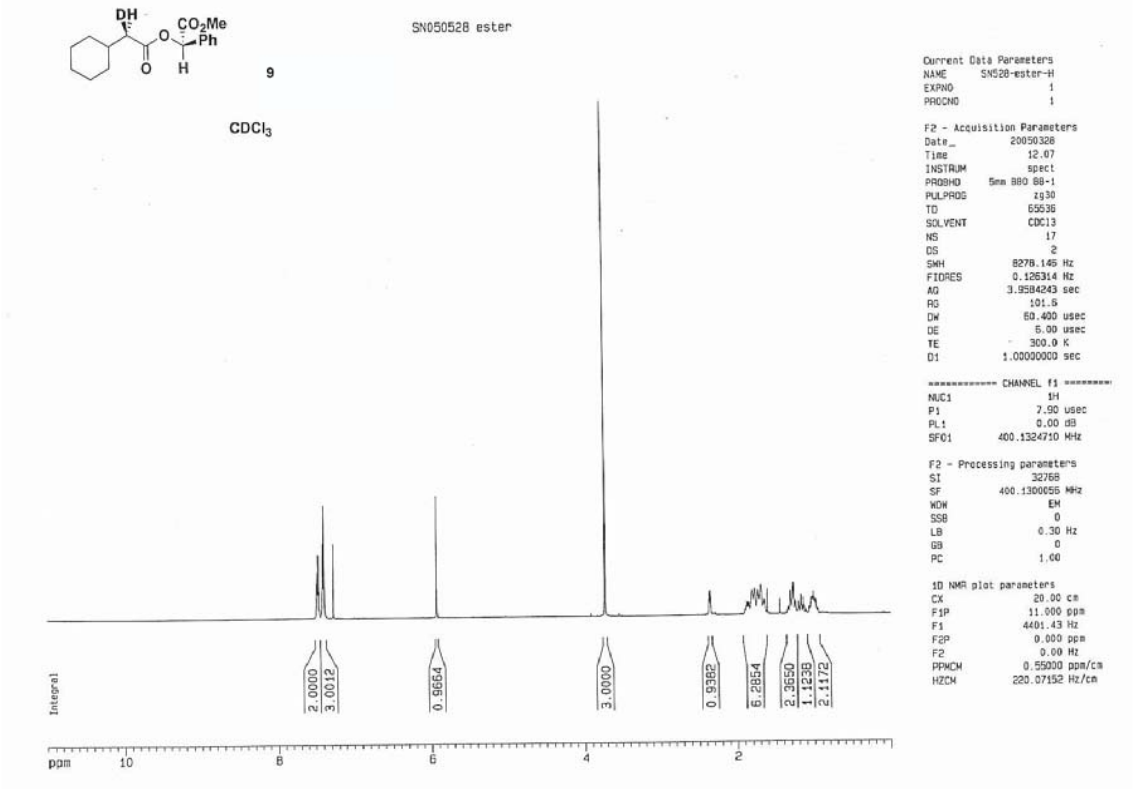

D
OH
O
7
CDCl3
SN050528 ozonolysis
Current Data Parameters
NAME SN528-03-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050326
Time 21.03
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 35.9
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm
Integral
5.2537
1.0000
0.9916
0.9942
1.1481
4.4133
1.1628
5.1300
1.3982
ppm
9
8
7
6
5
4
3
2
1


D
OH
O
7
CDCl3
SN050528 ozonolysis
Current Data Parameters
NAME SN528-03-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050326
Time 21.13
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 193
DS 4
SWH 25125.629 Hz
FIDRES 0.383367 Hz
AQ 1.3042164 sec
RG 2048
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127561 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 220.000 ppm
F1 22134.61 Hz
F2P 10.000 ppm
F2 1006.13 Hz
PPMCM 10.50000 ppm/cm
HZCM 1056.43395 Hz/cm
ppm
200
175
150
125
100
75
50
25


D
OH
O
8
SN050527 acid
CDCl3
Integral
0.8698
1.0000
6.1972
4.4089
2.4954
1 6 3 2
ppm
12
10
8
6
4
2
Current Data Parameters
NAME SN527-acid-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050326
Time 17.04
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 90.5
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300056 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 13.000 ppm
F1 5201.69 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.65000 ppm/cm
HZCM 260.08450 Hz/cm


D
OH
O
8
SN050527 acid
CDCl3
ppm
175
150
125
100
75
50
25
Current Data Parameters
NAME SN527-acid-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050326
Time 17.15
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 223
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042154 sec
RG 2048
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127492 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 210.000 ppm
F1 21126.68 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.50000 ppm/cm
HZCM 1056.43384 Hz/cm


SN050528 ester
9
C6D6
>90:10
Integral
1.9521
3.4702
3.0060
0.2526
0.9596
3.0000
0.9310
1.0347
2.0860
3.1538
2.2293
1.1368
2.1374
ppm
Current Data Parameters
NAME SN528-ester-H
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050329
Time 21.18
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 22
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 203.2
DW 60.400 usec
DE 6.00 usec
TE 712.3 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 9.68 usec
PL1 3.00 dB
SF01 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300443 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06502 Hz/cm


SN050528 ester
9
CDCl3
Integral
2.0000
3.0012
0.9664
3.0000
0.9362
6.2854
2.3650
1.1238
2.1172
ppm
Current Data Parameters
NAME SN528-ester-H
EXPNO 1
PROCNO 1
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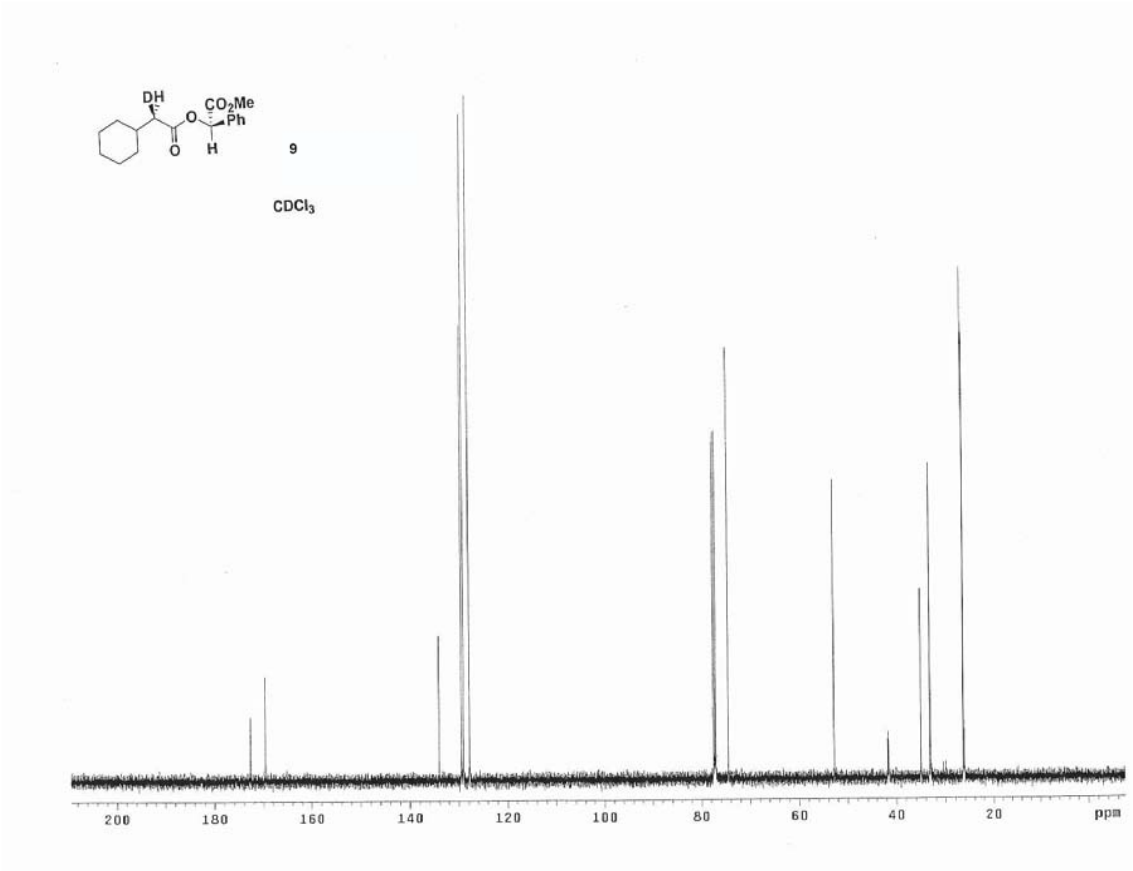
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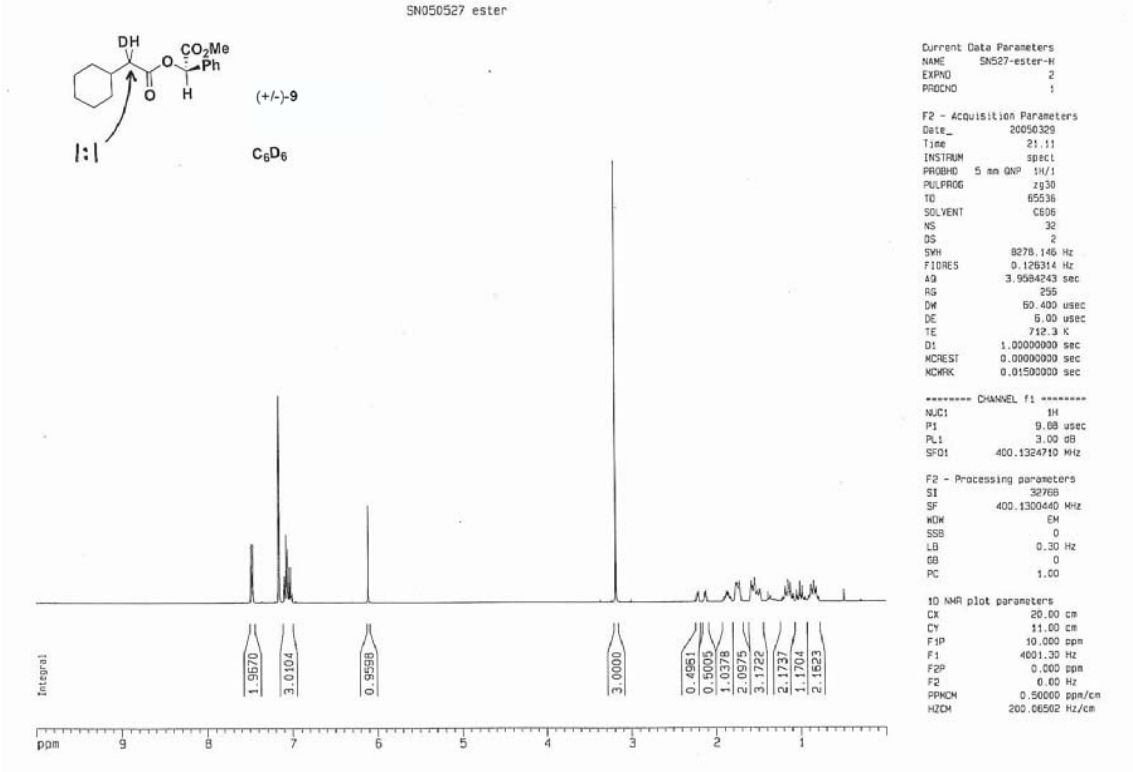
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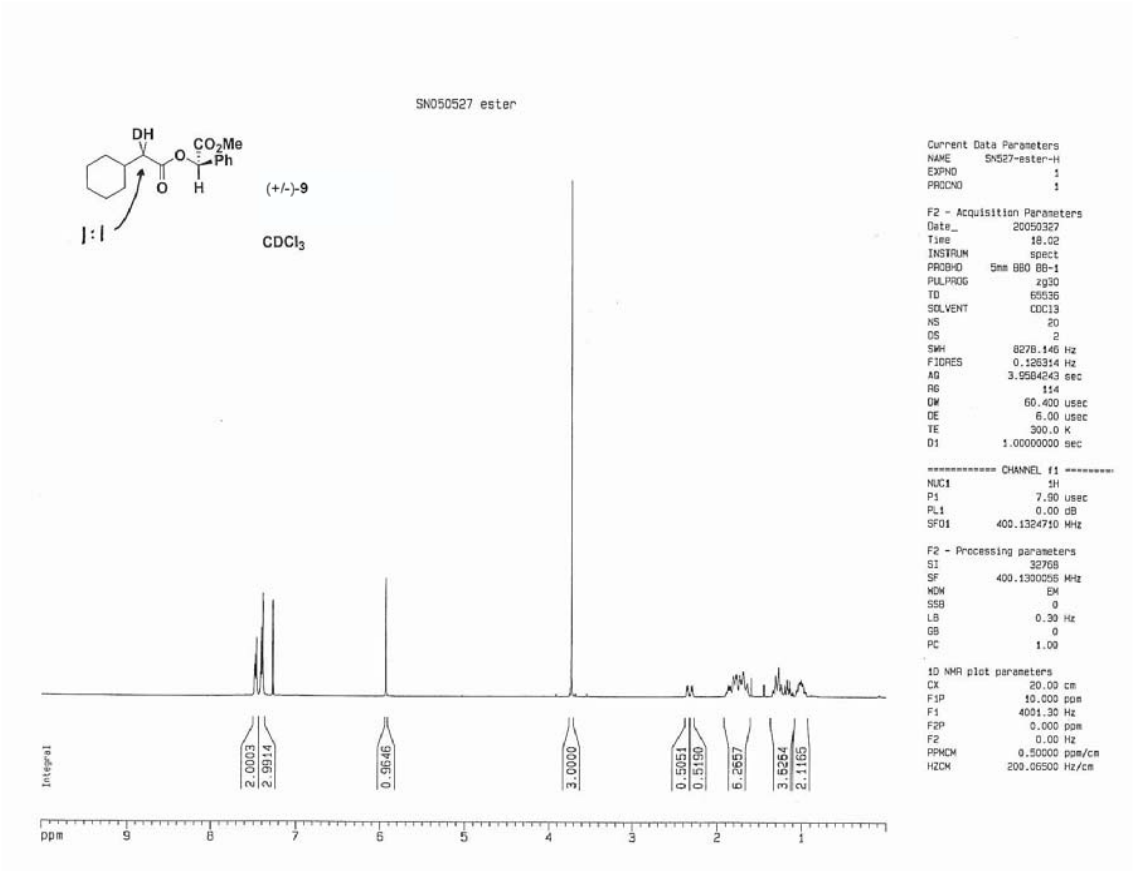

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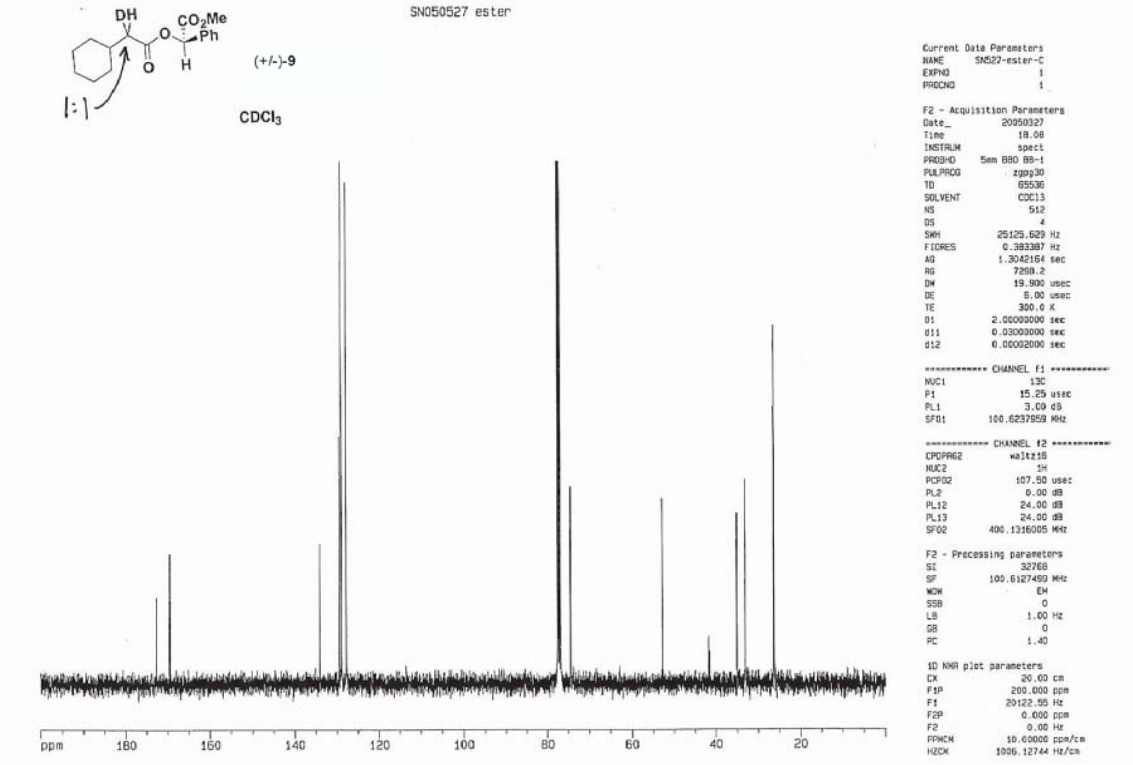

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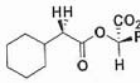

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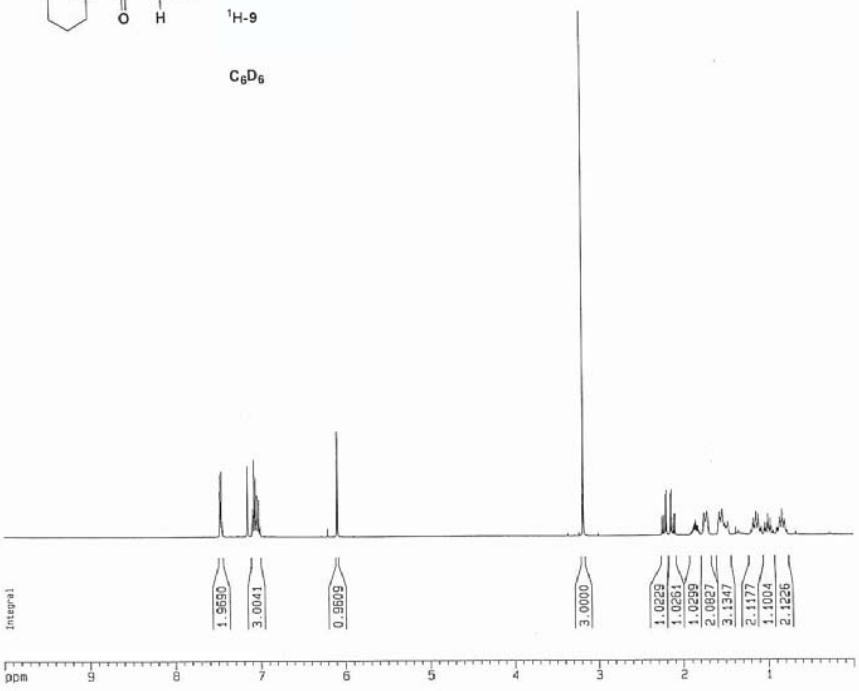
C_6D_6

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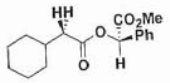
SN050526



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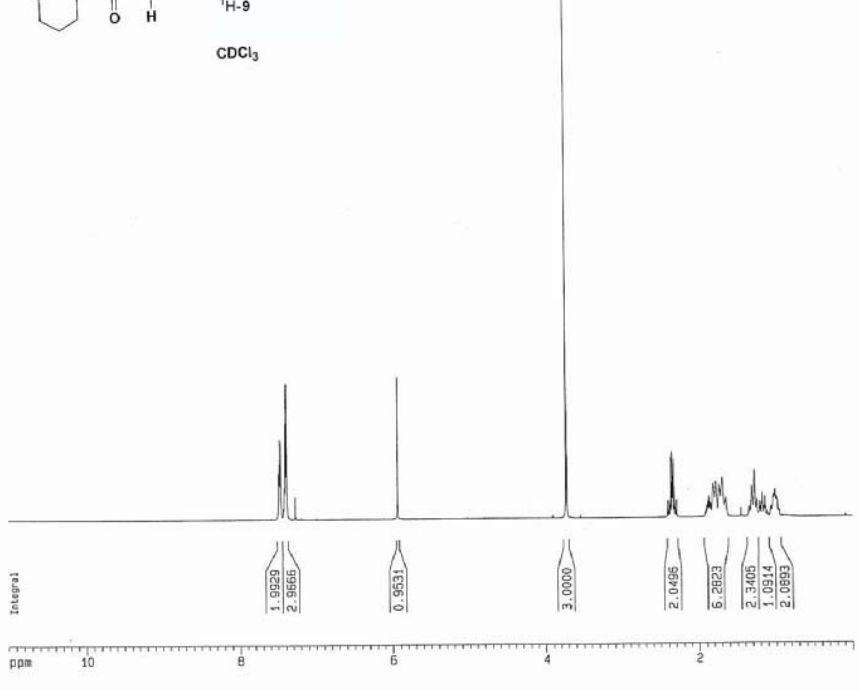


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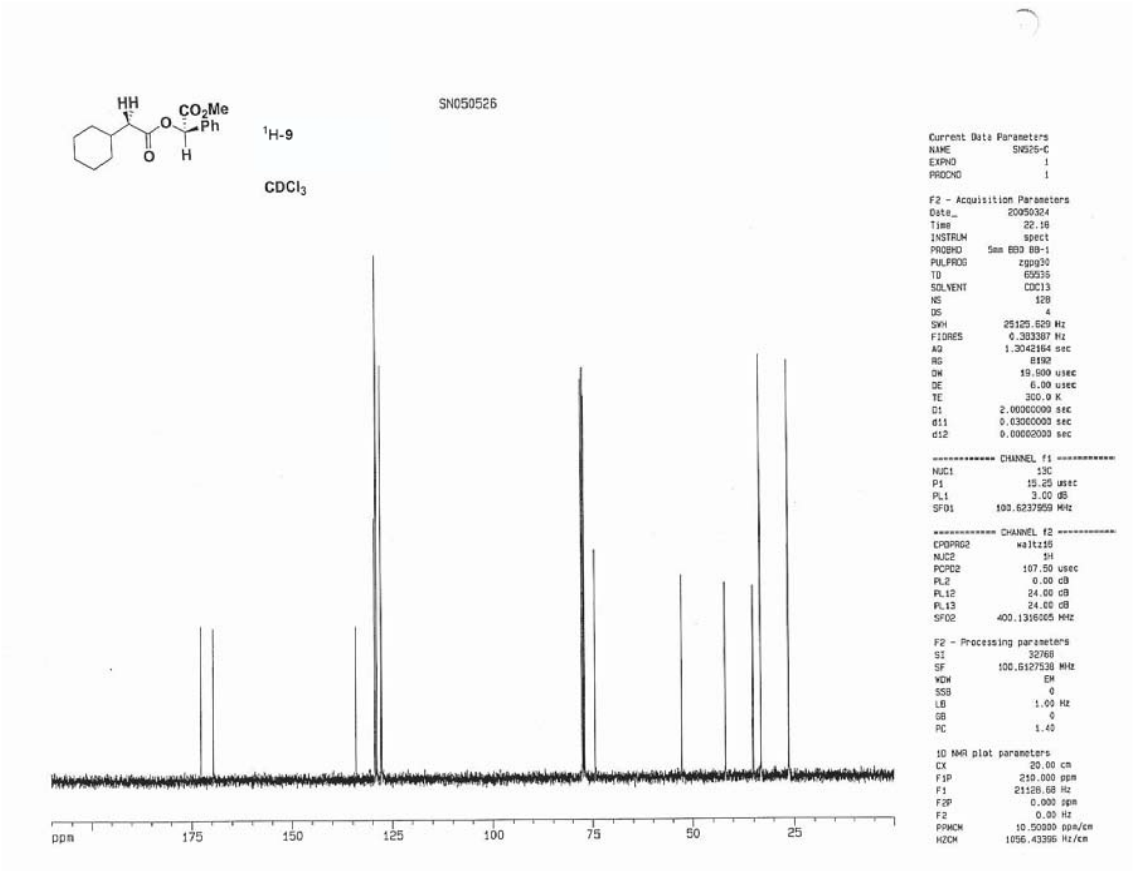
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Chapter 2

Nickel-Catalyzed Coupling of Alkenes and Aldehydes

Introduction

Alkenes are one of the most versatile, utilized, and readily available classes of functional groups. Simple alpha olefins are produced in megaton scale each year industrially, highlighting the importance of these organic feedstocks.[1] Several indispensable transformations utilize olefins, such as Ziegler-Natta polymerization,[2] the Heck reaction,[3a-e] Wacker oxidation,[3a] hydroformylation,[3a] hydrometallation,[3a] alkene cross-metathesis,[4] epoxidation[5] and dihydroxylation.[5]

Transition Metal-Catalyzed Coupling of Alkenes and Aldehydes

Transition metal-catalyzed intermolecular reductive and alkylative coupling reactions have emerged as useful methods for the preparation of alcohol and amine derivatives. Nickel, palladium, rhodium and ruthenium catalysts have been found to be particularly effective in the intermolecular coupling of alkynes, 1,3-enynes, 1,3-dienes, allenes, enoate esters, enones, and enals with aldehydes, ketones, epoxides, glyoxylate esters, and imines.[8-11] A variety of reducing agents have been used in these reductive couplings, such as triethylborane, organozinc reagents, organosilanes, and molecular hydrogen. As yet, however, simple, unactivated alkenes such as ethylene and 1-octene have not been reported to undergo analogous catalytic reductive coupling reactions.

As a part of our program directed toward developing C–C bond forming reactions of "off-the-shelf", simple starting materials, we became very interested in catalytic alkene–aldehyde coupling processes. Intramolecular versions of this transformation have been reported, such as transition metal-catalyzed cyclizations of enals and enones. For example, the titanium-catalyzed intramolecular reductive cyclization of enals and enones was first reported by Buchwald and Crowe.[12a-b] Recently Ogoshi has demonstrated a nickel-catalyzed cyclization of enones.[12c] α,ω-

Enals also undergo cyclization by way of a radical process[13] and also in a Lewis acid-catalyzed carbonyl-ene reaction.[7]

Intermolecular coupling of unactivated alkenes and aldehydes is commonly mediated by a transition metal (stoichiometric) or accomplished by way of a carbonyl-ene reaction.[7,15] An interesting process developed by Woerpel combined an alkene and an aldehyde through a silver-catalyzed silylene transfer reaction.[16]

Oxametallacycle of alkenes and aldehydes

Formation of an oxametallacycle through the oxidative coupling of simple alkenes and ketones has been observed with several transition metals such as titanium, zirconium and rhodium.[14] These studies suggested that transition metal-catalyzed, intermolecular coupling of alkenes and aldehydes would be feasible under the appropriate conditions. Ogoshi recently observed that Lewis acids such as a silyl triflate and trimethylaluminum facilitated the formation of an oxanickellacycle through cyclization of α,ω-enals and α,ω-enones.[17] We proposed that if the intermolecular coupling of an alkene and an aldehyde occurred, the nickel–alkyl bond could undergo a β-hydride elimination, followed by the removal of triflic acid from nickel to regenerate the nickel catalyst (Figure 1). This mechanistic framework also resembles that in the Heck reaction, a very important example of a catalytic coupling of an alkene and an electrophile.[3a-e]

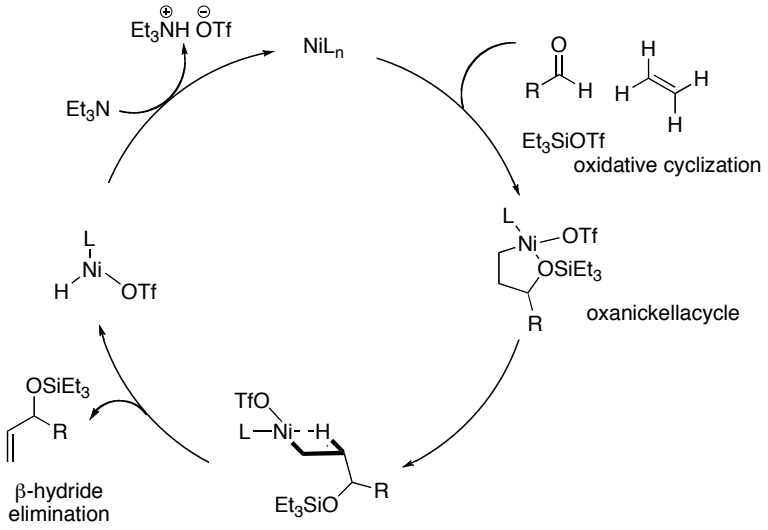


Figure 1. Proposed pathway for a nickel-catalyzed alkene–aldehyde coupling.

Carbonyl-Ene Reactions

The carbonyl-ene reaction has historically been the most direct method to combine simple alkenes and carbonyl compounds to provide homoallylic alcohol products. Recent efforts in this area have focused on asymmetric induction through the use of Lewis acids and chiral ligands, such as (bisoxazoline)CuX_2, (pybox)ScX_3, and (BINAP)TiX_2 complexes.[18a-18f] Typically the alkenes that are employed in intermolecular carbonyl-ene reactions are 1,1-disubstituted and trisubstituted olefins. With respect to the carbonyl component, electron-deficient enophiles such as glyoxylates, glyoxamides, and chloral are generally more efficient than simple aromatic and aliphatic aldehydes. In fact, since the report of the carbonyl-ene reaction in 1943[7a] there have been only a few scattered examples of intermolecular ene reactions between monosubstituted alkenes and simple aromatic and aliphatic aldehydes.[19]

To summarize, Lewis acid-catalyzed carbonyl-ene reactions are typically not feasible for the most readily available alkene and aldehyde building blocks. Part of the nickel-catalyzed coupling of alkenes and aldehydes described herein is thus complementary in scope to the carbonyl-ene

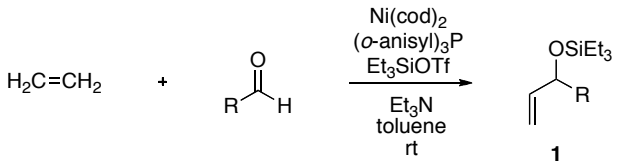
reaction; monosubstituted alkenes couple with simple aldehydes to provide a carbonyl-ene-type product in high yield.

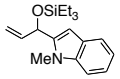
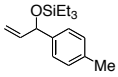
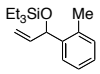
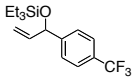
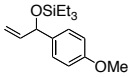
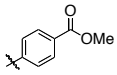
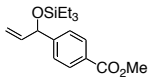
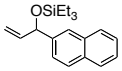
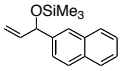
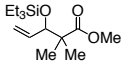
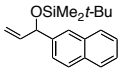
Nickel-Catalyzed Coupling of Ethylene and Aldehydes

Our investigations commenced with the simplest olefin, ethylene, and benzaldehyde. After a brief examination of phosphorous-based additives, we found that a combination of $Ni(cod)_2$, tris-(*o*-methoxyphenyl)-phosphine ((*o*-anisyl)$_3$P), triethylamine, and triethylsilyl triflate (Et_3SiOTf) promoted the coupling of ethylene with a variety of aldehydes. In all cases a triethylsilyl ether of an allylic alcohol is obtained in good to excellent yield (Table 1), providing ready access to a class of allylic alcohol derivatives that have been used in cross metathesis reactions, for example.[4]

Under 1 atm of ethylene, simple aromatic aldehydes such as benzaldehyde and *p*-tolylaldehyde undergo efficient coupling (entries 1–2). Ortho substitution on the aromatic aldehyde does not appear to deter the coupling process (entry 3), and notably, acid-sensitive heteroaromatic aldehydes such as 1-methyl-2-indolecarboxaldehyde (entry 8) and 2-furaldehyde (entry 9) are tolerated, even in the presence of Lewis acidic silyl triflates. As an additional advantage, other common silyl triflates can be used in the coupling reaction, providing orthogonal protection of the hydroxyl group when necessary (entries 5–7).

Table 1. Nickel-Catalyzed Coupling of Ethylene, Aldehydes, and Silyl Triflates[a]



entry	R (aldehyde)	R_3SiOTf	product	isolated yield (%)	entry	R (aldehyde)	R_3SiOTf	product	isolated yield (%)
1	Ph	Et_3SiOTf	**1a** 	82 (65) [b]	8		Et_3SiOTf	**1h** 	80
2	*p*-tolyl	Et_3SiOTf	**1b** 	88 (65) [b]	9	2-furyl	Et_3SiOTf	**1i** 	38
3	*o*-tolyl	Et_3SiOTf	**1c** 	93 (64) [b]	10 [f]		Et_3SiOTf	**1j** 	25
4	*p*-anisyl	Et_3SiOTf	**1d** 	95 (65) [c]	11 [f]		Et_3SiOTf	**1k** 	34
5	2-naphthyl	Et_3SiOTf	**1e** 	95 (83) [b]	12	piv	Et_3SiOTf	**1l** 	70
6	2-naphthyl	Me_3SiOTf	**1f** 	60	13		Et_3SiOTf	**1m** 	81 (40) [c, d]
7	2-naphthyl	*t*-$BuMe_2SiOTf$	**1g** 	67	14	cyclohexyl	Et_3SiOTf	**1n** 	25 [d] (34) [d, e]

[a] Standard procedure: $Ni(cod)_2$ (20 mol%) and (*o*-anisyl)$_3$P (40 mol%) were dissolved in 2.5 mL toluene under argon. Ethylene (balloon, 1atm) was substituted for argon. Triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 6-18 h at 23 °C. [b] (*o*-anisyl)$_3$P was replaced by Cy_2PhP. [c] (*o*-anisyl)$_3$P was replaced by Ph_3P. [d] Yields determined by ^1H NMR using DMF as a standard. [e] Conducted under 2 atm of ethylene. [f] Stirred at room temperature for 30 h.

Remarkably, sterically demanding tertiary aliphatic aldehydes such as pivaldehyde and 2,2-dimethyl-3-oxo-propionic acid methyl ester couple with ethylene with the same efficacy as benzaldehyde (entries 12 and 13). Enolizable aldehydes are not appropriate substrates in this system, however, since they react rapidly with the silyl triflate and triethylamine to form silyl enol ethers. The coupling of ethylene with cyclohexanecarboxaldehyde is fast enough, however, that a significant amount of coupling product is observed and can be isolated (entry 14).

Tris-(*o*-methoxyphenyl)-phosphine is the ligand of choice for the ethylene–aldehyde coupling. Other phosphines such as dicyclohexylphenylphosphine and triphenylphosphine provide lower yield under the same reaction conditions (entries 1–5, 13).

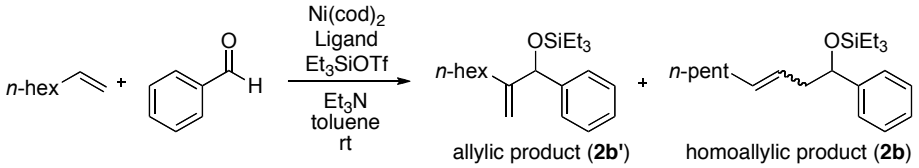
An interesting electronic effect is observed in these coupling reactions. Electron-rich aromatic aldehydes are more efficient substrates than electron-poor aromatic aldehydes. Among the four *para*-substituted aromatic aldehydes examined, electron-donating *para*-substituents (–Me and –OMe) improve the yield of the coupling reaction (entries 2 and 4). Electron-withdrawing *para*-substituents ($–CF_3$ and $–CO_2Me$) suffer from incomplete conversion, even after prolonged reaction time (entries 10–11). In such cases, products resulting from a pinnacol coupling are observed but are not observed in any other example.

Ligand-Dependent Regioselectivity in the Coupling of Terminal Alkenes and Aldehydes

The encouraging results in these ethylene–aldehyde coupling reactions prompted us to examine the scope of the alkenes in detail. Unlike ethylene, 1-octene can afford more than one possible coupling product depending on where the new carbon–carbon bond is formed. The examination of a series of ligands revealed several interesting observations regarding ligand-dependent regioselectivity.

Under similar reaction conditions as the ethylene–aldehyde cases, 1-octene and benzaldehyde undergo coupling in the presence of $Ni(cod)_2$, a ligand, triethylamine, and Et_3SiOTf. Two distinct types of coupling products are typically observed, namely a 1,1-disubstituted allylic alcohol product (**A**) and a homoallylic alcohol product (**H**). Different classes of phosphine ligands favor one or the other coupling products, as summarized in Tables 2 and 3.

Table 2. Ligand-Dependent Regioselectivity: Electron-Rich Phosphines[a]



entry	ligand	cone angle [b]	ν_{CO} [b]	yield (**2b'**) [c]	yield (**2b**) [c]	ratio (**2b'**:**2b**) [d]	combined yield (**2b'**+**2b**)
1	(n-Bu)$_3$P	132	1915	11%	27%	29:71	38%
2	(n-Oct)$_3$P	107		7%	14%	23:77	21%
3	(i-Pr)$_3$P	160	1915	11%	2%	85:15	13%
4	Cyp$_3$P			10%	3%	78:22	13%
5	Cy$_3$P	170	1915	13%	3%	81:19	16%
6	(t-Bu)$_3$P	182		7%	2%	78:22	9%
7	Cy$_2$PhP	162	1917	37%	16%	70:30	53%
8 [e]	Cy$_2$(o-tol)P	181		30%	5%	86:14	35%
9	Cy$_2$(o-Ph-Ph)P			32%	22%	60:40	54%
10 [f]	Cy$_2$FcP			14%	2%	88:12	16%

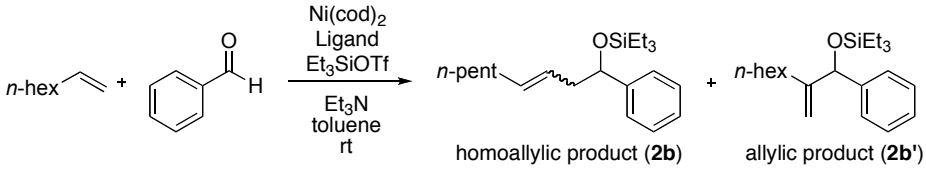
[a] Standard procedure: Ni(cod)$_2$ (20 mol%) and a ligand (40 mol%) were dissolved in 1.5 mL toluene. Alkene (500 mol%), triethylamine (600 mol%), the aldehyde (100 mol%, 0.25 mmol) and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] See ref. 20. [c] Yields determined by ^{1}H NMR using DMF as a standard. [d] Ratio was determined by ^{1}H NMR of the crude reaction mixture. [e] 48 h reaction time. [f] 1250 mol% alkene was used.

The ratio of the allylic to the homoallylic products is opposite for trialkylphosphines in which all alkyl groups are linear (entries 1 and 2), relative to those in which the three alkyl groups are branched (entries 3–5) or tertiary (entry 6). Among six trialkylphosphines with very similar electron-donating abilities,[20a] tri-*n*-butylphosphine, the smallest of the trialkylphosphines examined, favors the homoallylic alcohol product while tricyclohexylphosphine and tri-*t*-butylphosphine, the largest among these, favor the 1,2-disubstituted allylic product. However, these sterically demanding ligands are not nearly as effective, affording the coupling products in low yield.

Notably, replacing one of the alkyl substituent of the tricyclohexylphosphine with a phenyl ring dramatically improves the yield (53% vs 16%; Table 2, entries 5 and 7) with a slightly diminished A:H ratio. Other aryldicyclohexylphosphines also display a similar yield enhancement (entries 8 and 9, as compared to entries 4–6). The bulky and electron-rich dicyclohexylferrocenylphosphine, however, seems to be more closely related to tri-*t*-butylphosphine, (poor yield for both the allylic and homoallylic alcohol products, entry 10).[21] All of the sterically demanding dicyclohexylaryl derivatives examined favor the allylic alcohol product, and dicyclohexylphenylphosphine is the optimal ligand in terms of yield and selectivity. The pronounced ligand effects prompted us to examine other organophosphorus ligands (Table 3). Among the four triarylphosphine ligands with a similar cone angle but different *para*-substituents (entries 5–7 and 9),[20b,20c] tris-(*p*-trifluoromethyl-phenyl)-phosphine, the least electron-rich ligand of the four, has the highest H:A ratio (entry 9) whereas tri-*p*-tolylphosphine, the most σ-electron-donating among these four ligands, has the lowest H:A ratio (entry 5).

These data suggest that a higher H:A ratio can be achieved by decreasing the electron-donating ability of the phosphine ligand. In accord with this hypothesis, ethyldiphenylphosphinite ($(EtO)Ph_2P$) further improves the H:A ratio in the case of 1-octene and benzaldehyde (entry 8, 95:5). The hypothesis becomes even more convincing when the H:A ratio is plotted against the σ-electron-donating ability of various phosphines in Table 3 (Figure 2).[20] Very electron deficient phosphonites and phosphites are not effective ligands, however (entries 10 and 11). It should be noted that the cone angle of the ligands also affects the observed H:A ratio. Many of the less electron-rich ligands that favor the homoallylic product in Table 3 are also among the smaller ligands.

Table 3. Ligand-Dependent Regioselectivity: Electron-Poor Phosphines[a]

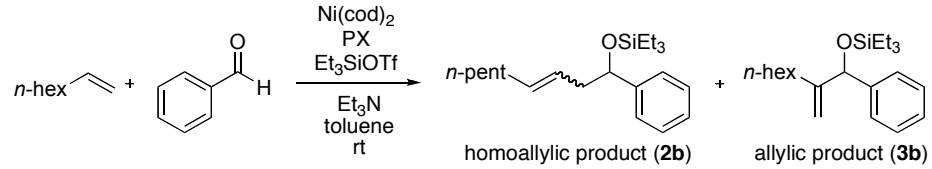


homoallylic product (**2b**) allylic product (**2b'**)

entry	ligand	cone angle [b]	ν_{CO} [b]	combined yield [c] (**2b**+**2b'**)	ratio (**2b**:**2b'**) [d]	*E*:*Z* (**2b**) [d]
1 [e]	Cy_2PhP	162	1917	73	29:71	n.d.
2	$CyPh_2P$	153	1917	84	75:25	91:9
3	$(o\text{-anisyl})_3P$	194	1919	70	83:17	80:20
4	$FcPh_2P$	173		70	88:12	81:19
5	$(p\text{-tol})_3P$	145	1920	78	92:8	67:33
6	Ph_3P	145	1922	73	92:8	67:33
7	$(p\text{-F-Ph})_3P$	145	1924	74	92:8	57:43
8	$(EtO)Ph_2P$	133	1926	81	95:5	75:25
9	$(p\text{-}CF_3\text{-Ph})_3P$	145	1929	44	>95:5	69:31
10	$(EtO)_2PhP$	121	1932	20	>95:5	89:11
11	$(PhO)_3P$	128	1951	<5	n.d	n.d.

[a] Standard procedure: $Ni(cod)_2$ (20 mol%) and a ligand (40 mol%) were dissolved in 2.5 mL toluene. Alkene (1 mL), triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol) and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] See ref. 20. [c] Yields were determined by ^1H NMR using DMF as a standard. [d] Ratio was determined by ^1H NMR after the products were treated with TBAF. [e] 48 h reaction time.

Based on the results of this study, we surmised that the coupling product ratio is determined by a combined effect of the electron-donating ability and the cone angle of the phosphine ligands. High H:A ratios can be achieved by using less electron-rich phosphines with small cone angle such as $(EtO)Ph_2P$ while high A:H ratios can be obtained by using electron-rich phosphines with a large cone angle such as Cy_2PhP.[22]



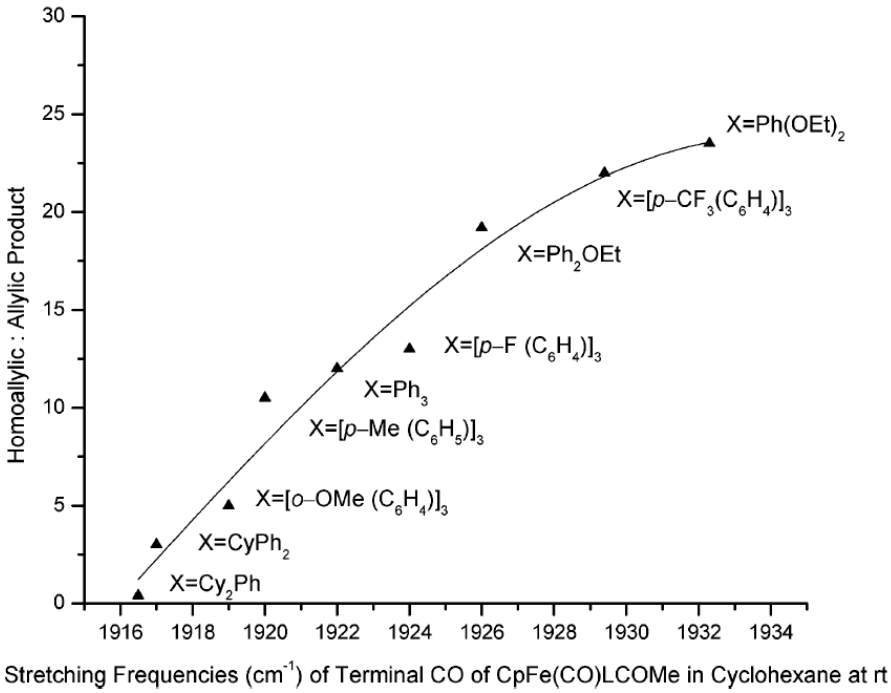


Figure 2. Plot of H:A ratio against the σ-electron-donating ability of various phosphines.[20]

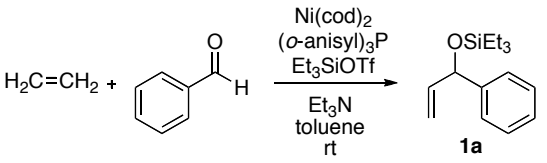
Effects of the Base

Tertiary amines are the optimal bases for the nickel-catalyzed coupling of alkenes and aldehydes. Among different types of amine bases examined in ethylene couplings, only tertiary amines provide >20% yield of coupling products (Table 4, entries 1 and 3). Amines that likely are able to interact with nickel to a greater degree, such as pyridine (Table 4, entry 5 and Table 6, entry 6), are not effective. No coupling products are detected when inorganic bases are used in place of triethylamine (Table 4, entries 6–8).

Tertiary amines were further examined in the 1-octene coupling reaction (Tables 5–6), and triethylamine was consistently superior to other tertiary amines (Table 5, 1–4 and Table 6, 1–5).

Tertiary amines smaller or larger than triethylamine compromised the yield of the coupling reaction (Table 5, entries 2–4).

Table 4. Effect of Bases in the Ethylene–Benzaldehyde Coupling[a]



1a

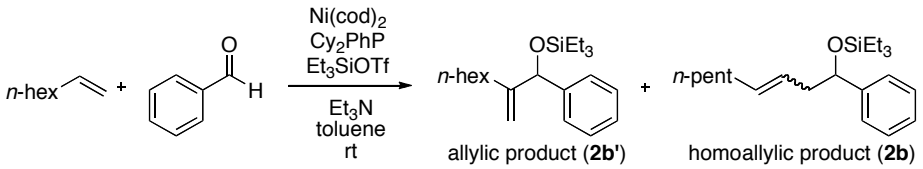
entry	base	yield [b]
1	Et_3N	77
2	Et_2NH	3
3	*N*-methylpyrrolidine	36
4	proton sponge	10
5	pyridine	12
6 [c]	K_3PO_4	<5
7	K_3CO_3	<5
8	Cs_2CO_3	<5

[a] Standard procedure: $Ni(cod)_2$ (20 mol%) and (*o*-anisyl)$_3$P (40 mol%) were dissolved in 2.5 mL toluene under argon. Ethylene (balloon, 1 atm) was substituted for argon. A base (600 mol%), benzaldehyde (100 mol%, 0.5 mmol), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] Yields were determined by ^1H NMR using DMF as a standard. [c] Benzaldehyde was replaced by 2-naphthaldehyde and the reaction was run at 0.25 mmol scale.

The nature of the tertiary amines in determining the yield deserves further comment. It appears that a balance of the nucleophilicity, basicity, and steric bulk of the amine base is required for the coupling reaction to occur efficiently. Amines can compete with the phosphorus ligand, alkene, and aldehyde for a coordination site on nickel. A more nucleophilic (σ-electron-donating) or smaller amine might hinder the coordination of any of the other required components to the nickel catalyst. For instance, the less nucleophilic *N*-methylmorpholine (Table 6, entry 3) provides a better yield than *N*-methylpiperidine (Table 6, entry 4).

In summary, triethylamine is the best base for the nickel-catalyzed coupling of alkenes and aldehydes, probably because of a combination of low coordinating ability and appropriate basicity.

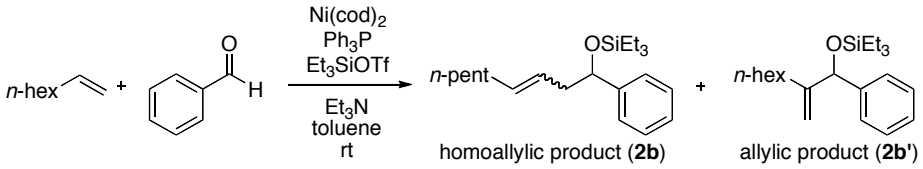
Table 5. Effect of Bases in the 1-Octene–Benzaldehyde Coupling (Cy_2PhP)[a]



entry	base	combined yield (**2b'**+**2b**) [b]	ratio (**2b'**:**2b**) [c]
1	Et_3N	61%	78:22
2	$Et(i\text{-}Pr)_2N$	10%	60:40
3	Cy_2NMe	20%	60:40
4	*N*-methylpyrrolidine	7%	71:29
5	2,6-lutadine	12%	58:42

[a] Standard procedure: $Ni(cod)_2$ (20 mol%) and Cy_2PhP (40 mol%) were dissolved in 1.5 mL alkene. A base (600 mol%), benzaldehyde (100 mol%, 0.1 mmol), and Et_3SiOTf (100 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] Yields were determined by ^1H NMR using DMF as a standard. [c] Ratio was determined by ^1H NMR of the crude reaction mixture.

Table 6. Effect of Bases in the 1-Octene–Benzaldehyde Coupling (Ph_3P)[a]



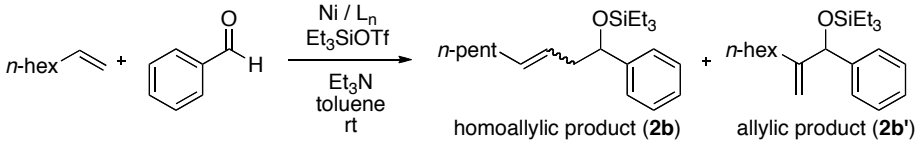
entry	base	combined yield (**2b**+**2b'**) [b]	ratio (**2b**:**2b'**) [b]	ratio (*E*/*Z*) [c] (**2b**)
1	Et_3N	64%	92:8	87:13
2	Cy_2NMe	35%	>95:5	71:29
3	*N*-methylmorpholine	25%	94:6	69:31
4	*N*-methylpiperidine	<5%	n.d.	n.d.
5	*N*-methylpyrrolidine	<5%	n.d.	n.d.
6	DMAP	<5%	n.d.	n.d.

[a] Standard procedure: $Ni(cod)_2$ (20 mol%) and Ph_3P (40 mol%) were dissolved in 2.5 mL toluene. 1-octene (1 mL), a base (600 mol%), benzaldehyde (100 mol%, 0.5 mmol), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] Yields and ratios were determined by ^1H NMR using DMF as a standard. [c] Ratio was determined from the desilylated product by ^1H NMR.

Source of Nickel

Since the precatalyst $Ni(cod)_2$ has two chelating diene ligands (1,5-cyclo-octadiene), other nickel(II) precatalysts without alkene ligands were examined, including $Ni(Ph_3P)_4$, $Ni(acac)_2/Ph_3P/DIBAL$, $Ni(Ph_3P)_2Cl_2/n$-BuLi, and $Ni(Ph_3P)_2Br_2/n$-BuLi (Table 7). Only the $Ni(acac)_2/Ph_3P/DIBAL$ system is as efficient as $Ni(cod)_2/Ph_3P$ (entry 3). $Ni(Ph_3P)_4$ is saturated with phosphine ligand, and perhaps alkene coordination to the nickel catalyst is thus inhibited. Similarly, $Ni(cod)_2/Cy_2PhP$ is more efficient than $Ni(acac)_2/Cy_2PhP/DIBAL$ and $Ni(Cy_2PhP)_2Cl_2/n$-BuLi (Table 8).[23] Therefore $Ni(cod)_2$ was used in all subsequent investigations.

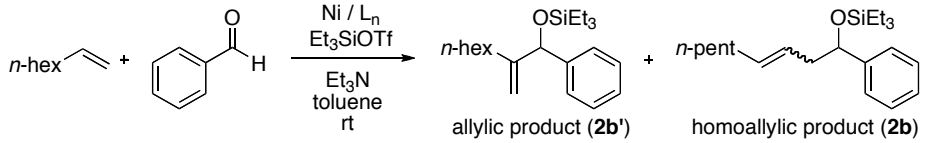
Table 7. Examination of Other Nickel Precatalysts[a]



entry	catalyst	yield (**2b**) [b]	yield (**2b'**) [b]	ratio (**2b**:**2b'**) [c]	combined yield [b] (**2b**+**2b'**)
1	$Ni(cod)_2$ / Ph_3P	78%	6%	93:7	84%
2	$Ni(Ph_3P)_4$	41%	3%	93:7	44%
3	$Ni(acac)_2$ / Ph_3P / DIBAL	72%	5%	93:7	77%
4	$Ni(Ph_3P)_2Cl_2$ / *n*-BuLi	32%	2%	94:6	34%
5	$Ni(Ph_3P)_2Br_2$ / *n*-BuLi	<5%	<5%	n.d.	<5%

[a] Standard procedure: The nickel precatalyst system (20 mol%) was dissolved in 2.5 mL toluene. The alkene (1 mL), triethylamine (600 mol%), the aldehyde (100 mol%, 0.5 mmol), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 48 h at 23 °C. [b] Yields were determined by ^1H NMR using DMF as a standard. [c] Ratios were determined by ^1H NMR of the crude reaction mixture.

Table 8. Examination of Other Nickel Precatalysts[a]



entry	catalyst	yield (**2b'**) [b]	yield (**2b**) [b]	ratio (**2b'**:**2b**) [c]	combined yield [b] (**2b'**+**2b**)
1	$Ni(cod)_2$ / Cy_2PhP	52%	21%	71:29	73%
2 [d]	$Ni(cod)_2$ / Cy_2PhP	53%	20%	73:27	73%
3	$Ni(acac)_2$ / Cy_2PhP / DIBAL	39%	16%	71:29	55%
4	$Ni(Cy_2PhP)_2Cl_2$ / *n*-BuLi	21%	7%	75:25	28%

[a] Standard procedure: The nickel precatalyst system (20 mol%) was dissolved in toluene. The alkene (500 mol%), triethylamine (600 mol%), the aldehyde (100 mol%), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 48 h at 23 °C. [b] Yields were determined by ^1H NMR using DMF as a standard. [c] Ratios were determined by ^1H NMR of the crude reaction mixture. [d] 1 mL 1-octene was used.

Substrate Scope

Applying the results of the studies of ligand and base effects, the substrate scope of the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates was next examined (Tables 9–12). In general, ethylene and monosubstituted alkenes are superior substrates in this coupling reaction, while 1,1-disubstituted alkenes and acyclic 1,2-disubstituted (*cis* or *trans*) alkenes are significantly less reactive. Trisubstituted alkenes do not react under the standard reaction conditions.

The Ni–$EtOPh_2P$ system efficiently catalyzes the coupling of monosubstituted alkenes and simple aromatic aldehydes such as benzaldehyde (Table 9). While the couplings of ethylene with most aldehydes usually take less than 8 h to reach completion, those involving monosubstituted alkenes typically require more than 18 h (entries 2–3). Nevertheless, with $EtOPh_2P$ as the ligand, nickel catalyzes the coupling of several monosubstituted alkenes and aldehydes in excellent

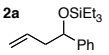
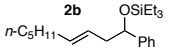
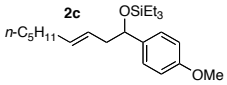
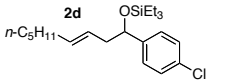
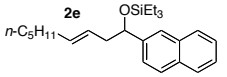
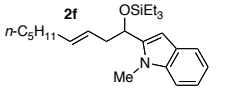
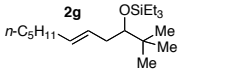
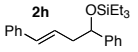
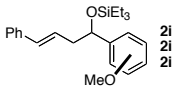
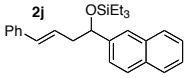
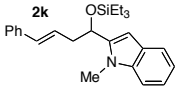
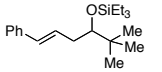
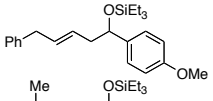
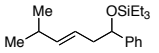
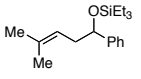
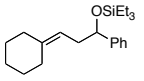
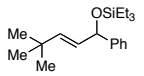
yield. The reaction is also highly regioselective and *E*/*Z* selective, favoring an *E*-homoallylic alcohol product.

Aromatic aldehydes (Table 9, entries 2, 6, 9, 12), heteroaromatic aldehydes (entries 7 and 13), and sterically demanding aldehydes (entries 8 and 14) are excellent coupling partners with monosubstituted alkenes, affording an *E*-homoallylic alcohol derivative as the major product and an allylic alcohol derivative as the minor product, with a selectivity >95:5 in most cases. Monosubstituted aromatic aldehydes of all substitution patterns are tolerated (*ortho*-, *meta*-, and *para*-, entry 10). Aldehydes with an electron-donating substituent in the *para* position (*p*-MeO–, entry 4) are more reactive than aldehydes with an electron-withdrawing group in the same position (Cl–, entry 5), consistent with the observation in the ethylene–aldehyde couplings. The product derived from *p*-chlorobenzaldehyde can be elaborated further by way of a cross-coupling reaction.

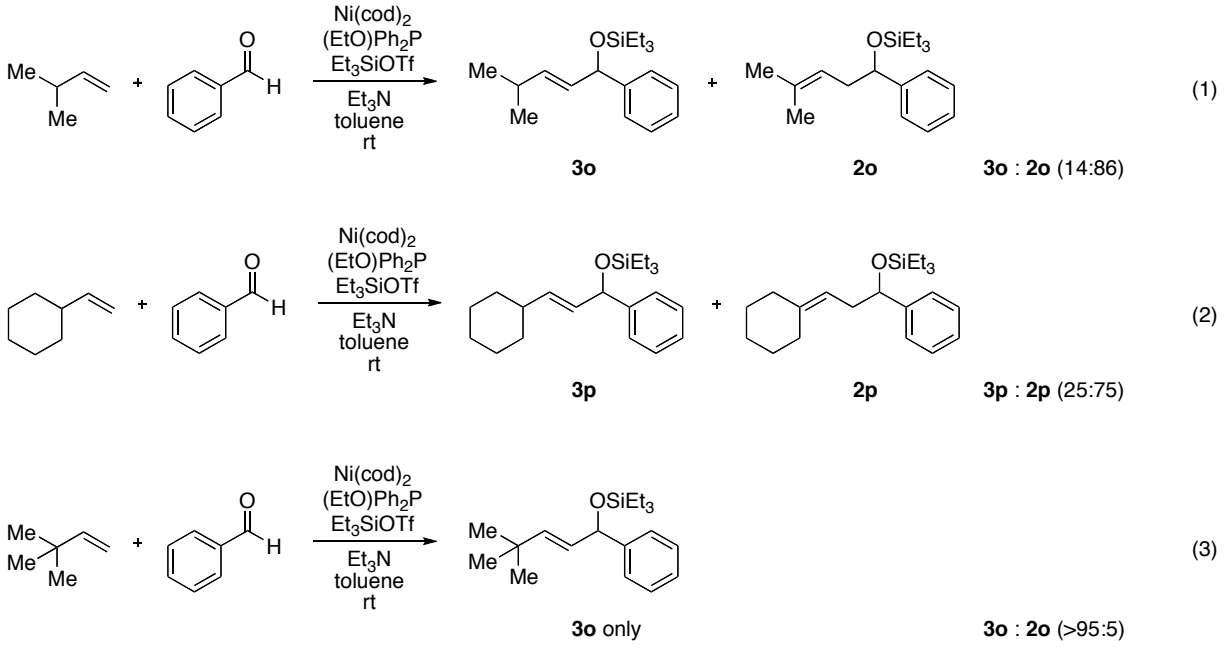
Allylbenzene is an excellent substrate, and the homoallylic products are useful styrene derivatives. The *E*-isomer is observed exclusively. Oligomerization of the coupling product is not observed, as evidenced by the excellent yield of the coupling reactions (entries 9–14).

Linear monosubstituted olefins such as propene and 1-octene are not the only terminal olefins that can participate in this nickel-catalyzed reaction (entries 1, 2, 9, 15). Alkenes with substitution at the homoallylic position couple with benzaldehyde in similar regioselectivity and *E*/*Z* selectivity as in the case of 1-octene (entry 16, as compared to entry 2).

Table 9. Homoallylic Alcohols from Nickel-Catalyzed Alkene–Aldehyde Couplings[a]

entry	alkene	aldehyde	major product (**2**)	yield (%) (**2**:**2'**) [b,c]	*E*:*Z* (**2**) [b]
1 [d]	Me	PhCHO	**2a** 	73 (89:11)	n.a.
2	*n*-C_6H_{13}	PhCHO	**2b** 	85 (95:5)	75:25
3 [e]				72 (>95:5)	75:25
4 [e]		*p*-anisaldehyde	**2c** 	85 (>95:5)	75:25
5 [e]		*p*-Cl(C_6H_4)CHO	**2d** 	37 (>95:5)	74:26
6 [f]		2-naphthaldehyde	**2e** 	88 (>95:5)	70:30
7		1-methyl-2-indole-carboxaldehyde	**2f** 	56 (>95:5)	83:17
8 [f]		*t*-BuCHO	**2g** 	64 (>95:5)	78:22
9	Ph	PhCHO	**2h** 	86 (92:8)	>95:5
10		*o*-anisaldehyde *m*-anisaldehyde *p*-anisaldehyde	 **2i** (ortho) **2i** (meta) **2i** (para)	78 (92:8) 98 (92:8) 99 (92:8)	>95:5 >95:5 >95:5
11 [f,g]		*p*-anisaldehyde	**2i** (para)	98 (92:8)	>95:5
12 [f]		2-naphthaldehyde	**2j** 	88 (95:5)	>95:5
13		1-methyl-2-indole-carboxaldehyde	**2k** 	57 (>95:5)	>95:5
14		*t*-BuCHO	**2l** 	65 (>95:5)	78:22
15	Ph	*p*-anisaldehyde	**2m** 	91 (92:8)	69:31
16	Me Me	PhCHO	**2n** 	82 (>95:5)	81:19
17	Me Me		**2o** 	95 (86:14) [h]	n.a.
18			**2p** 	99 (75:25) [h]	n.a.
19	Me Me Me		**3q** 	14 (>95:5) [i]	n.a.

[a] Standard procedure: (entries 1-8, 15-18): To a solution of $Ni(cod)_2$ (0.1 mmol) and $EtOPPh_2$ (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (0.5 mL), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et_3SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO_2). Entries 9-14: Ph_3P was used in place of $EtOPPh_2$. [b] Yields were determined by ^1H NMR using DMF as a standard. [c] See Supporting Information for structures of the minor products (**2a'**-**2p'**). [d] Propene (1 atm) was used in place of Ar. [e] Reaction time 18 h. [f] Reaction temperature 35 °C. [g] Fivefold larger reaction scale. [h] ratio of **2**:**3**. [i] ratio of **3**: (**2q**+**2q'**).



Alkenes with substituents at the allylic position, on the other hand, afford different results. A homoallylic alcohol derivative is still the major coupling product in the coupling of 2-methyl-butene (entry 17) and vinylcyclohexane (entry 18) with benzaldehyde. However, the minor product is an *E*-1,3-disubstituted allylic alcohol, rather than the usual 1,2-disubstituted allylic alcohol obtained from the coupling of unbranched alkenes (eqs 1–2). The coupling of 3,3-dimethyl-butene and benzaldehyde yields exclusively 1,3-disubstituted allylic alcohol product (eq 3). This observation maybe important in understanding the mechanism of these transformations, which is discussed in more detail in the discussion section below.

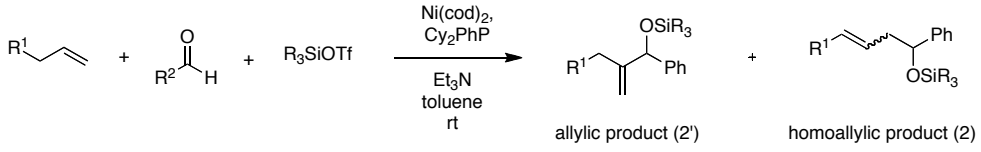
Allylic, rather than homoallylic alcohol derivatives can be prepared by the nickel-catalyzed coupling of alkenes and aldehydes simply by substituting Cy_2PhP for $EtOPh_2P$ (Table 10). Hence, propene couples with naphthaldehyde to provide the allylic alcohol product in good yield and with the highest selectivity (Table 10, entry 1). In contrast to the Ni–$EtOPh_2P$ system, the homoallylic alcohol is the minor product in this case.

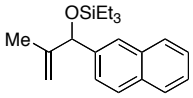
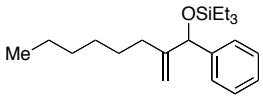
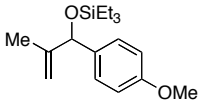
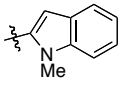
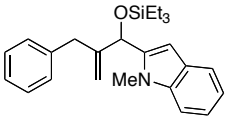
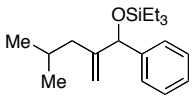
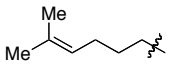
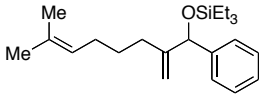
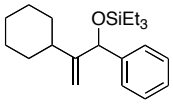
Once again, aromatic aldehydes and heteroaromatic aldehydes couple with straight chain monosubstituted alkenes in good yield (entries 1–2, 4). Electron-donating *p*-anisaldehyde is, as before, more reactive than benzaldehyde (entries 1 and 3). Therefore, based on all the data that we gathered so far, it seems to be the trend that generally electron-donating aldehydes are more reactive than electron-poor aldehydes.

There are, however, some differences in the substrate scope of the alkene in the Ni–Cy_2PhP system relative to that of the Ni–$EtOPh_2P$ system. While branching at the homoallylic position of the alkene does not affect the coupling efficiency (entry 5), branching at the allylic position significantly attenuates the yield of the allylic alcohol product (entry 7). For example, vinylcyclohexane has a dramatically lower A:H ratio (entry 7), and the homoallylic alcohol and a 1,3-disubstituted allylic alcohol are the major products.

In a competition study, benzaldehyde undergoes coupling with a monosubstituted alkene selectively in the presence of a trisubstituted alkene (entry 6); the trisubstituted double bond is stable to the reaction conditions. Carbocyclization is not observed, nor do we observe any isomerization of the trisubstituted double bond in the coupling product. This result enables the use of a trisubstituted double bond as a masked version of other functional groups.

Table 10. Allylic Alcohols from Nickel-Catalyzed Alkene–Aldehyde Couplings[a]



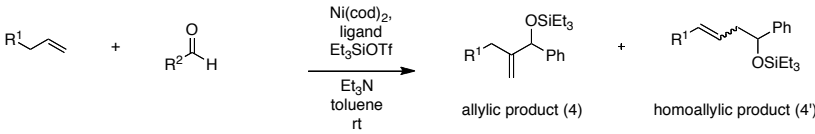
entry	R^1 (alkene)	R^2 (aldehyde)	R_3SiOTf	major product		yield (%) [b] (**2**+**2'**)	ratio (**2'**:**2**) [c]
1 [d]	Me	naphthyl	Et_3SiOTf		**2r'**	82	84:16
2	*n*-hexyl	Ph	Et_3SiOTf		**2b'**	70	71:29
3 [d]	Me	*p*-anisyl	Et_3SiOTf		**2s'**	95	82:18
4	Ph		Et_3SiOTf		**2k'**	56 [e]	80:20
5	isobutyl	Ph	Et_3SiOTf		**2n'**	62	71:29
6		Ph	Et_3SiOTf		**2t'**	72	71:29
7	*c*-hexyl	Ph	Et_3SiOTf		**2p'**	5 [f]	n.d.

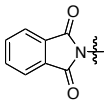
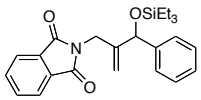
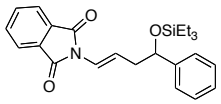
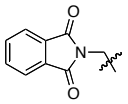
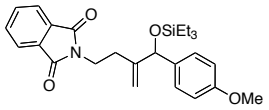
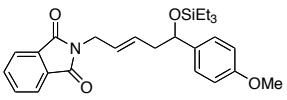
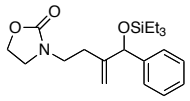
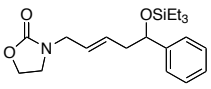
[a] Standard procedure: $Ni(cod)_2$ (20 mol%), Cy_2PhP (40 mol%) were dissolved in 2.5 mL toluene. Excess alkene, triethylamine (600 mol%), the aldehyde (100 mol%, 0.5mmol), and Et_3SiOTf (175 mol%) were added. The reaction mixture was stirred 18 h at 23 °C. [b] Unless specified, isolated yield of all coupling products. [c] Ratios were determined by ^1H NMR of the crude reaction mixture. [d] 1 atm propene (balloon) was used and naphthaldehyde (100 mol%) was mixed with $Ni(cod)_2$ and Cy_2PhP before the addition of toluene. [e] Yields were determined by ^1H NMR using DMF as a standard. [f] Isolated yield of the allylic product **2p'**.

Given that heteraromatic aldehydes are competent substrates in these coupling reactions, we became interested in the effect of heteroatoms on the alkene. *N*-allylphthalimide, *N*-homoallylphthalimide and *N*-homoallyloxazolidinone undergo coupling in both the Ni–Cy_2PhP and Ni–$EtOPh_2P$ systems (Table 11, entries 1–3). In particular, the coupling of *N*-allylphthalimide and benzaldehyde in the Ni–$EtOPh_2P$ system affords an enamine that appears to be stable to the coupling conditions. In contrast, allylbenzoate and homoallylbenzoate esters are

much less efficient (Table 12, entries 1–4). A small amount of the allylic product is detected only with homoallylbenzoate (entry 2). When the benzoate group is further away from the terminal double bond, a better yield of the desired coupling product is observed (entry 3). These findings suggest an interaction of the heteroatoms on the alkenes to the nickel catalyst. We propose that since the oxygen on the phthalimide is less nucleophilic, it does not bind to the nickel as tightly as the benzoate oxygen. Therefore the coupling of *N*-allylphthalimide occurs more efficiently than allylbenzoate (Table 11, entry 1 and Table 12, entry 1). As the benzoate becomes further away from the double bond, the benzoate is less likely to coordinate to the nickel catalyst, and the reactivity of the alkene is restored (Table 12, entry 3). The silyl ether-tethered alkene (entry 4) does not experience the heteroatom attenuation effect, likely for the same reason as the benzoate ester in entry 3.

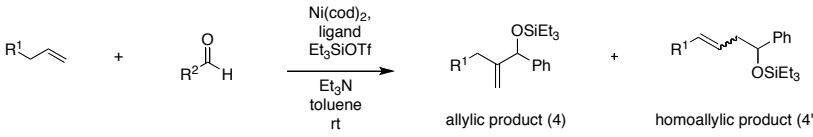
Table 11. Coupling of Nitrogen-Containing Alkenes with Aldehydes[a]

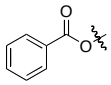
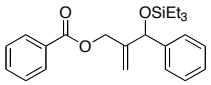
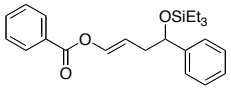
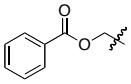
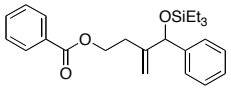
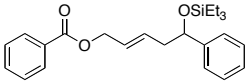
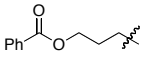
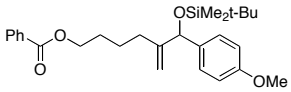
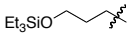
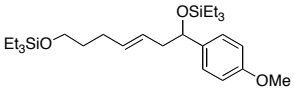


entry	R^1 (alkene)	R^2 (aldehyde)	ligand	major product		yield (%) [b]	ratio (**4**:**4'**) [b]	ratio (*E*:*Z*) [c]
1		Ph	Cy_2PhP		**4a**	67	74:26	-
			$(EtO)Ph_2P$		**4a'**	43	12:88	60:40
2		*o*-anisyl	Cy_2PhP		**4b**	54	71:29	-
			Ph_3P		**4b'**	76	<5:95	83:17
3		Ph	Cy_2PhP		**4c**	60	83:17	-
			$(EtO)Ph_2P$		**4c'**	28	10:90	n.d.

[a] Standard procedure: To a solution of $Ni(cod)_2$ (0.1 mmol) and ligand (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (1.5 mmol), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et_3SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO_2). [b] Determined by ^1H NMR of the crude reaction mixture using DMF as a standard. [c] The ratio was determined by ^1H NMR of the mixture of *E* and *Z* homoallylic alcohols after the silyl group of the coupling product was removed by TBAF.

Table 12. Coupling of Oxygen-Containing Alkenes with Aldehydes[a]



entry	R^1 (alkene)	R^2 (aldehyde)	ligand	major product		yield (%) [b]	ratio (**4**:**4'**) [b]	ratio (*E*:*Z*) [c]
1		Ph	Cy_2PhP		**4d**	<5	n.d.	-
			$(EtO)Ph_2P$		**4d'**	<5	n.d.	n.d.
2 [e]		Ph	Cy_2PhP		**4e**	21	n.d.	-
			$(EtO)Ph_2P$		**4e'**	<5	n.d.	n.d.
3		*o*-anisyl	Cy_2PhP		**4f**	44 [d]	73:27	-
4 [e]		*o*-anisyl	$(EtO)Ph_2P$		**4g**	66	7:93	50:50

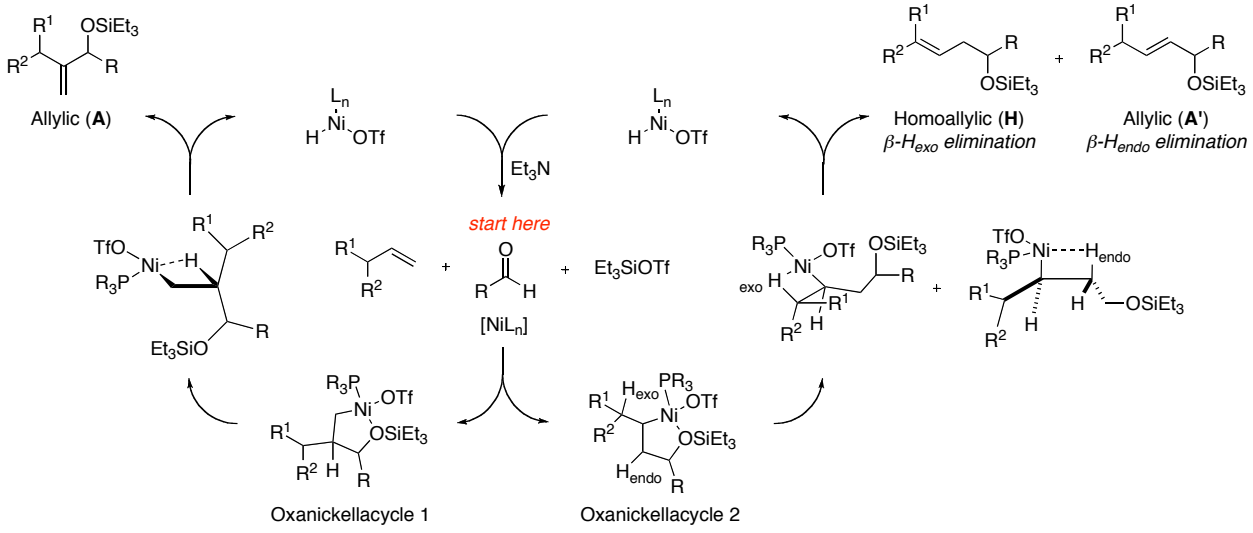
[a] Standard procedure: To a solution of $Ni(cod)_2$ (0.1 mmol) and ligand (0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added the alkene (2.5 mmol), triethylamine (3.0 mmol), the aldehyde (0.5 mmol), and Et_3SiOTf (0.875 mmol). The mixture was stirred 48 h at room temperature and purified by chromatography (SiO_2). [b] Determined by ^1H NMR of the crude reaction mixture using DMF as a standard. [c] The ratio was determined by ^1H NMR of the mixture of *E* and *Z* homoallylic alcohols after the silyl group of the coupling product was removed by TBAF. [d] Isolated yield. [e] 1.5 mmol alkene was used.

Discussion

General Mechanistic Framework

We believe that the nickel species that catalyzes the alkene–aldehyde coupling reactions above is not functioning simply as a Lewis acid. We propose that the coupling reaction proceeds through the formation of oxanickellacycle from a nickel(0) complex (Scheme 1). A *syn* β-hydride elimination would afford the coupling product and a nickel–hydride species, analogous to a Heck reaction.[3a-c] Finally, base-promoted reductive elimination of the nickel–hydride intermediate could regenerate the nickel(0) catalyst. Note that a base-mediated β-elimination of the oxanickellacycle via an E2-like mechanism cannot be completely ruled out. Based on our observations and in analogy to the Heck reaction,[3a-c] we believe the nickel–hydride pathway is operative (see below).

Scheme 1

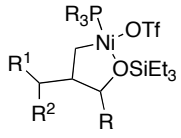
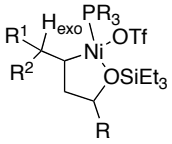
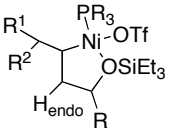
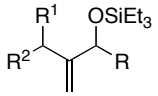
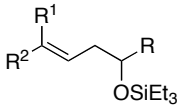
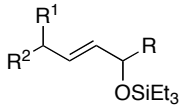


Ligand Effects

The interactions of nickel with the ligand, alkene, and aldehyde govern the assembly of the oxanickellacycle, and the oxanickellacycle in turn determines the product distribution. Scheme 2

summarizes the factors that control the product ratio in the alkene–aldehyde coupling reactions. In general, use of large phosphines favors the allylic alcohol product (**A)** (e.g., the coupling of 1-octene with benzaldehyde with Cy_2PhP as ligand yielded allylic alcohol as the major product.) The use of small phosphines (Bu_3P, $(EtO)Ph_2P$, Ph_3P, etc) on the other hand affords the homoallylic alcohol (**H)** as the major product.

Scheme 2

Ligand	large cone angle and electron rich (e.g., Cy_2PhP)	small cone angle and electron poor (e.g., $(EtO)Ph_2P$)	
Alkene	alkene with no branching at the allylic position tolerated (e.g., propene, 1-octene)	branching at the allylic position tolerated (e.g., vinylcyclohexane)	
Aldehyde	smaller substituents (e.g., R = Ph)	larger substituents (e.g., R = 2-naphthyl, *t*-butyl)	
Oxanickellacycle	 Oxanickellacycle 1	 Oxanickellacycle 2	 Oxanickellacycle 2
Coupling product	 Allylic (**A**)	 Homoallylic (**H**)	 Allylic (**A'**)

Size of Coupling Partners

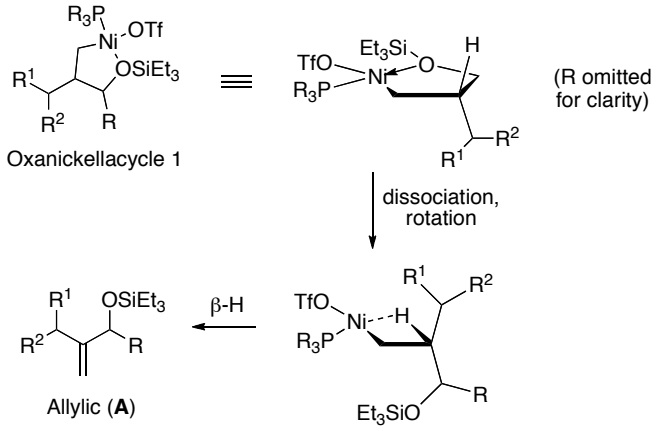
The substituents on the alkene and aldehyde also affect the ratio of the coupling products. The alkene substituents can either be closer to the ligand or the aldehyde substituent in the

oxanickellacycle. Allylic alcohol product **A** is obtained in a significant amount when the alkene has no branching at the allylic position. On the other hand, branching at the allylic position does not affect the coupling process when a small ligand, such as $(EtO)Ph_2P$, is used, and homoallylic allylic alcohol **H** is formed in good yield. 3,3-dimethyl-1-butene, a sterically demanding monosubstituted alkene with no allylic hydrogen, provides 1,3-disubstituted allylic alcohol **A'** as the sole product.

A large substituent on aldehyde favors the production of homoallylic alcohol. Less than 5% allylic alcohol product is observed when propene or 1-octene is coupled with pivaldehyde with Cy_2PhP as the ligand. In the following sections, we propose a detailed model consistent with all of these observations.

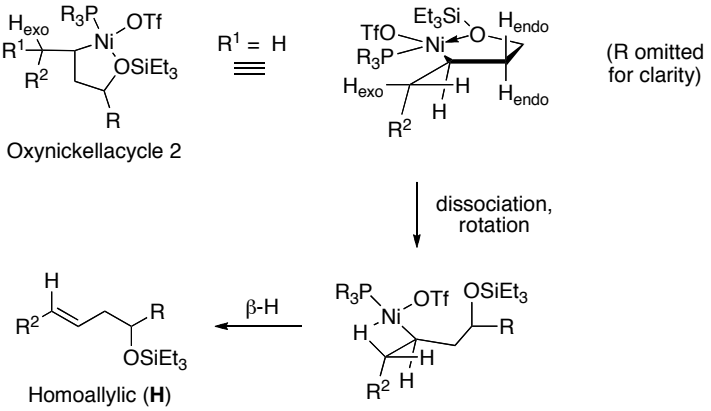
We begin by examining oxanickellacycle 1 in more detail (Scheme 3). The β-hydrogen of the oxanickellacycle 1 is not aligned with the C–Ni bond. Since β-hydride elimination generally occurs in the *syn* orientation, The $–OSiEt_3$ group must dissociate from nickel to allow bond rotation such that the β-hydrogen can align with C–Ni bond. At this stage, β-hydride elimination occurs and allylic product **A** is formed. The larger the phosphine ligand relative to the aldehyde substituent, the more likely oxanickellacycle 1 dominates because the alkene substituent would thus avoid severe steric repulsion with this ligand. The data shown in Table 2 support this proposal; the A:H ratio increases with the cone angle of the trialkylphosphine.

Scheme 3



Oxanickellacycle 2 accounts for the formation of homoallylic alcohol **H** and allylic alcohol **A**'. Examination of oxanickellacycle 2 reveals that although the β-hydrogen in the oxanickellacycle (H_{endo}) is not aligned with the C–Ni bond, there are β-hydrogens outside the oxanickellacycle (H_{exo}) that are appropriately poised for β-hydride elimination once a free coordination site is available (Scheme 4).[3e] The preferred conformation would align R^2 of the alkene *trans* to the C–C bond of the oxanickellacycle 2. Dissociation of one of the ligand on nickel provides a free coordination site for the *syn* β-hydride elimination to occur and provides the *E*-homoallylic alcohol **H**.

Scheme 4



In order for the unusual allylic alcohol (**A'**) to form, the β-hydrogens in the oxanickellacycle (H_{endo}) must be eliminated instead of the *exo*-β-hydrogen (H_{exo}). Such a process requires dissociation of $–OSiEt_3$ and maybe favored when the *exo*-β-hydrogen is not aligned with the C–Ni bond, or when there is no *exo*-β-hydrogen (Scheme 5).

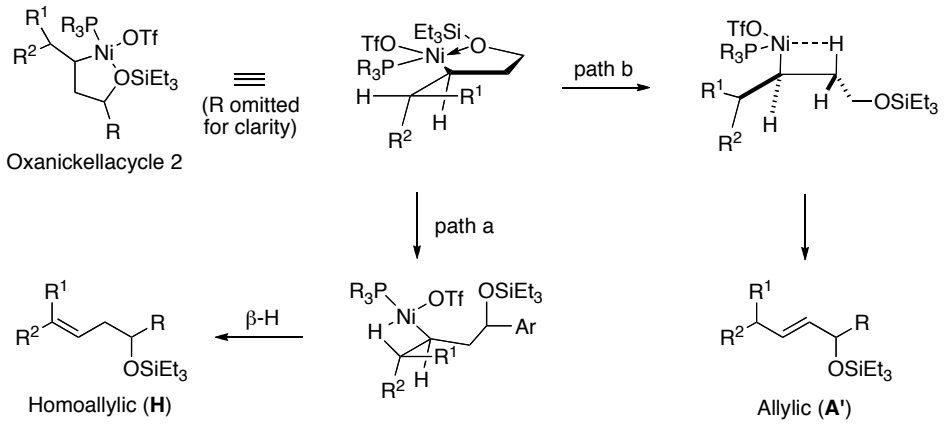
The coupling of vinylcyclohexane and benzaldehyde serves as a good example to illustrate the formation of 1,3-disubstituted allylic alcohol **A'** (Scheme 5). Neither R^1 nor R^2 of vinylcyclohexane is a hydrogen atom, and hence the allylic position is very sterically encumbered. The usual allylic alcohol product **A** is not favored because the large substituent of vinylcyclohexane will not be accommodated next to the aldehyde substituent (R) in oxanickellacycle 1 (Scheme 3) due to severe steric repulsion.

Experimental data support this theory: The coupling of vinylcyclohexane with benzaldehyde using Cy_2PhP as ligand yields only 5% of the allylic alcohol product **A** (Table 10, entry 7, as compared with other unbranched alkenes in Table 10, entries 1–6). Using a smaller ligand, such as $(EtO)Ph_2P$, the large substituents in vinylcyclohexane can be accommodated by being closer to the ligand than to the aldehyde substituent, favoring oxanickellacycle 2 (Scheme 5). The *exo*-β-hydrogen of the oxanickellacycle, when aligned to with C–Ni bond, induces an unfavorable steric interaction between the cyclohexyl group and the C–C bond of the oxanickellacycle. Therefore the rate of β-hydride elimination from the *exo*-β-hydrogen decreases, and that of the *endo*-β-hydrogen increases, resulting in a greater amount of the unusual *E*-allylic product **A'**. The *E*-double bond geometry of **A'** is obtained by minimizing steric repulsion during the β-H elimination step.

Alkenes without an allylic hydrogen cannot afford homoallylic alcohol products in the nickel-catalyzed alkene–aldehyde coupling reaction. For example, 3,3-dimethyl-1-butene, with no

allylic hydrogen, couples with benzaldehyde to give exclusively *E*-1,3-disubstituted allylic alcohol product (**A'**).[24] Also, it appears that the steric bulk of the *tert*-butyl group renders formation of oxanickellacycle 1 extremely difficult, eliminating the possibility of affording 1,1-disubstituted allylic alcohol product **A**.

Scheme 5



The proposed mechanistic framework is also supported by Ogoshi's observation that cyclization of an α,ω-enal to form an oxanickellacycle is facilitated by the presence of a silyl triflate.[17] A control experiment confirms that without silyl triflate, no coupling product is observed.[22]

The evidence for the β-hydride elimination as the next step is the observation of isomerization and dimerization (hydrovinylation) of the starting olefins, which suggests the presence of a nickel–hydride (Ni–H) species, likely formed by a β-hydride elimination.[3d] The requirement of a base in this catalyst system also supports the presence of a Ni–H species. A β-hydride elimination and subsequent base-assisted removal of triflic acid (reductive elimination) from the Ni–H species regenerates the Ni(0) catalyst (Scheme 1) and may also minimize side reactions by suppressing the presence of the Ni–H species.

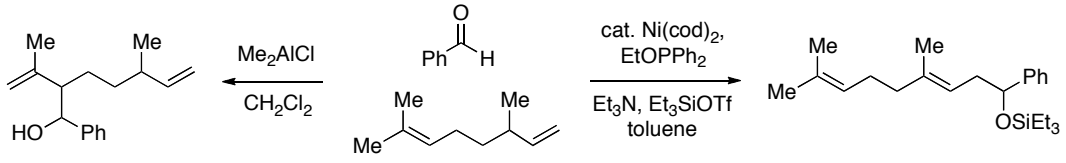
We do not believe the direct precursor to the oxanickellacycle in this coupling reaction is a cationic nickel (II) species. Ni^{2+}, Pd^{2+}, and Pt^{2+} catalysts have been reported to be effective Lewis acids for carbonyl-ene reactions.[18g-i] The nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates affords carbonyl-ene-type products in good yield, but the substrate scope is entirely different from that of a Lewis acid-catalyzed carbonyl-ene reaction. While the three cationic group 10 transition metal catalysts are effective in the carbonyl-ene reaction of the more nucleophilic alkenes such as 1,1-disubstituted alkenes and the more electrophilic aldehydes such as glyoxylate esters, they do not promote the coupling of monosubstituted alkenes and simple aldehydes.

The nickel catalyst system has the opposite alkene and aldehyde substrate scopes relative to those of the carbonyl-ene reaction. The nickel–phosphine catalyst selectively reacts with monosubstituted olefins, and we observe that electron rich aldehydes, such as *p*-anisaldehyde, consistently provide better yield than benzaldehyde and electron-deficient aldehydes. Although this coupling reaction readily provides homoallylic alcohol products corresponding to a carbonyl-ene reaction, it is more likely that the oxanickellacycle precursor is a Ni(0) species, and probably not just a Lewis acid catalyst.

To illustrate the difference between the Ni(0)–phosphine system and a Lewis acid system, β-citronellene and benzaldehyde were coupled under two conditions; using a classical Lewis acid and the Ni–$EtOPh_2P$ conditions.[6b] As expected, the Lewis acid-catalyzed reaction reacts at the more nucleophilic trisubstituted double bond. For the Ni–$EtOPh_2P$ system, however, the monosubstituted double bond reacts preferentially because it is the kinetically more accessible double bond. These observations are also in accord with many palladium-catalyzed reactions of

alkenes (such as Wacker oxidation and alkene hydroamination), in that a monosubstituted double bond is usually more reactive than a more substituted double bond.[3a]

Scheme 6



5a

40% yield

> 95:5 site selectivity

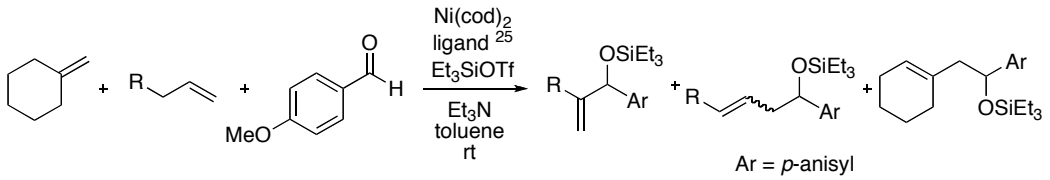
5b

75% yield (71:29 *E/Z*)

> 95:5 site selectivity

The difference in substrate scope between the nickel-catalyzed alkene–aldehyde coupling and the carbonyl-ene reaction is further illustrated by competition experiments between a monosubstituted alkene and a 1,1-disubstituted alkene (Scheme 7).[25-26] Equal amounts of allylbenzene and methylenecyclohexane were included in the otherwise standard coupling conditions. The coupling reaction was highly selective; 92% of all of the coupling products detected are derived from allylbenzene. The presence of methylenecyclohexane does not change the H:A ratio of the coupling products of allylbenzene (as compared to Table 9, entry 10). A similar trend is observed between 1-octene and methylenecyclohexane (as compare to Table 9, entry 4), but the presence of excess methylenecyclohexane in the reaction mixture seems to lower the yield of the coupling reaction. This lower efficiency might be due to competition for a coordination site on nickel between monosubstituted alkenes and methylenecyclohexane.

Scheme 7. Competition Experiments Between Mono- and 1,1-Disubstituted Alkenes[25-26]



alkene	vs		vs	
yield (H:A)	88% (92:8)	7% (n.a.)	64% (95:5)	5% (n.a.)
ratio	(92:8)		(92:8)	

Further evidence that supports the notion that the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates does not involve a carbonyl-ene reaction mechanism is that ethylene, with no allylic hydrogen, also participates in this coupling reaction using the same Ni–phosphine catalyst system.

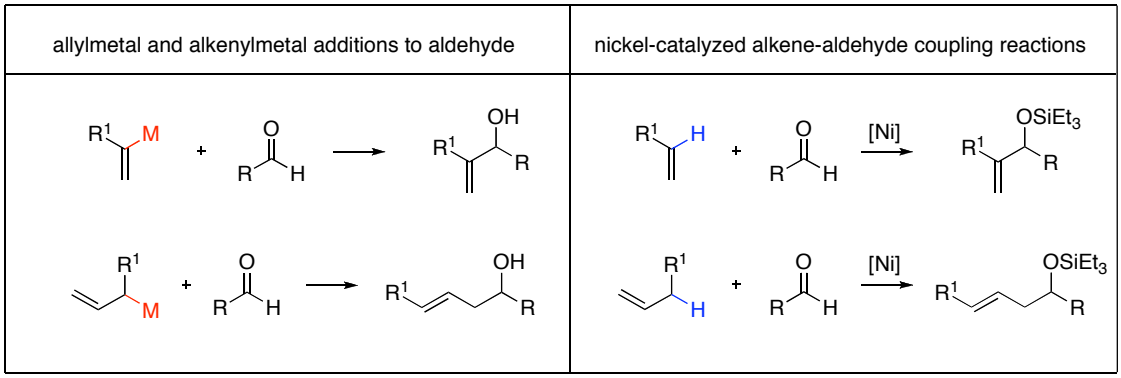
Common side reactions in these nickel-catalyzed reactions are the dimerization (hydrovinylation)[27] and isomerization[28] of the starting olefin. One explanation for the requirement of excess alkenes in this coupling reaction is that the terminal alkene is isomerized to an internal alkene and that this new internal alkene is not reactive in the coupling process. While isomerization of olefin is common in the coupling reaction, hydrovinylation of olefins is observed in small amounts only when the alkene–aldehyde coupling process is not efficient. The presence of a base in the coupling reaction may keep the Ni-H concentration to a minimum, thus suppressing some of these side reactions.

Conclusion

The nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates represents a new alternative to both allylmetal reagents and alkenylmetal reagents (Scheme 8). The parent allylmetal reagent and vinylmetal reagent can now be replaced by propene and ethylene,

respectively, using the nickel-catalyzed processes as described herein. The preparation of a terminal, monosubstituted alkene is generally more straightforward than that of the allylmetal species such as those shown in Scheme 8.

Scheme 8



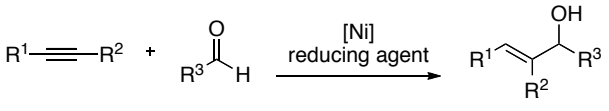
The transformation in this nickel-catalyzed alkene–aldehyde coupling reaction is, in effect, a C–H functionalization reaction of the alkene, involving addition to an aldehyde. Mechanistically, an entirely different process likely occurs, rather than oxidative addition into a C–H bond that would be expected to have a relatively high energy activation barrier.

Unlike the related transition metal-catalyzed reductive coupling reactions developed by our group and others,[8] the nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates described in this work is not an overall reductive process (Scheme 9). Thus, the coupling of an alkene and an aldehyde, in theory, does not require a third component to form the allylic or homoallylic alcohol derivatives. However, both alkenes and aldehydes are generally unreactive toward each other. Thus, activation of either or both components is necessary. The Lewis acid-catalyzed carbonyl-ene reaction serves as a good example. Intermolecular carbonyl-ene reaction between monosubstituted alkene and unactivated aldehydes such as acetaldehyde is not a practical method under thermal conditions. The presence of a Lewis acid, however, allows the coupling to proceed at room temperature. The Lewis acidic nature of silyl triflate in the nickel-

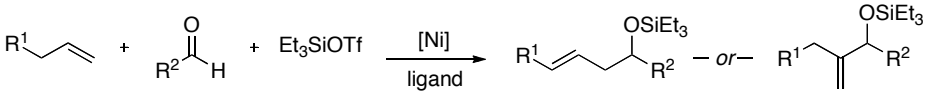
catalyzed alkene–aldehyde coupling reaction likely plays a similar role, providing sufficient activation of the electrophile for the nickel catalyst to promote the coupling reaction.

Scheme 9

Nickel-Catalyzed Alkyne–Aldehyde Coupling Reactions (Reductive):



Nickel-Catalyzed Alkene–Aldehyde Coupling Reactions (Non-Reductive):



The two classes of the nickel-catalyzed coupling reactions of alkene, aldehyde, and silyl triflate presented here represent unique, non-reductive coupling processes that allow the preparation of derivatives of allylic alcohols or homoallylic alcohols from readily available olefins. The selectivity for these two products is highly ligand dependent, and high selectivity in either direction is possible. These coupling reactions are mechanistically different from Lewis acid-catalyzed carbonyl-ene reactions, and conceptually, alkenes serve as substitutes for both allylmetal reagents and alkenylmetal reagents.

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3) (a) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J.; John Wiley & Sons: New York, 1995. (b) Review of the related Heck reaction and palladium–hydride chemistry: Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E.-i.: Wiley-Interscience: New York, 2002. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**,

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5) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed; Wiley-VCH: New York, 2000.

6) Preliminary communications of this work: (a) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc*. **2005**, *127*, 14194–14195. (b) Ho, C.-Y.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc*. **2006**, *128*, 5362–5363.

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22) A set of four control experiments in which Ni(cod)$_2$, ligand, silyl triflate and the base was each removed from the ethylene–benzaldehyde coupling reaction. No coupling product was detected in any of the four experiments.

23) (a) Nickel:phosphine ratio is also important. A 1:2 Ni:phosphine ratio provides a higher yield than a 1:1 Ni:phosphine ratio in the coupling reaction. (b) No coupling was observed when Ni(cod)$_2$ / Ph_3P was replaced with Pd(Ph_3P)$_4$.

24) Coupling of 3,3-dimethyl-1-butene and benzaldehyde under the standard coupling condition (EtOPh_2P, rt, 48h) affording an *E*-1,2-allylic alcohol product in 14% yield.

25) Procedure of the competition experiment: To a solution of Ni(cod)$_2$ (0.1 mmol) and the ligand (Ph_3P or (EtO)Ph_2P, 0.2 mmol) in toluene (2.5 mL) at 23 °C under Ar were added a

monosubstituted alkene (2.5 mmol) , methylenecyclohexane (2.5 mmol), triethylamine (3.0 mmol), *p*-anisaldehyde (0.5 mmol), and triethylsilyl triflate (0.875 mmol). The mixture was stirred 48 h at room temperature. The yields and ratios were determined by ^{1}H NMR of the crude reaction mixture. Ph_3P was the ligand in the reaction between allylbenzene and methylenecyclohexane. $(EtO)Ph_2P$ was the ligand in the reaction between 1-octene and methylenecyclohexane.

26) As a control experiment, methylenecyclohexane (300 mol%) was coupled with *p*-anisaldehyde under standard condition ($Ni(cod)_2$, $EtOPh_2P$, Et_3SiOTf, Et_3N) to give 13% yield of the homoallylic alcohol product. To determine whether the formation of this coupling product requires $Ni(cod)_2$, another control experiment was carried out by stirring methylenecyclohexane, *p*-anisaldehyde and Et_3SiOTf at room temperature. No alkene–aldehyde coupling product was observed.

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Experimental Section

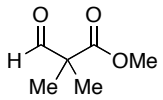
General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled from calcium hydride. Aromatic aldehydes were purchased from Aldrich Chemical Co. and used as received. Other aldehydes were distilled and saturated with nitrogen before use. Bis(cyclooctadienyl)nickel(0) ($Ni(cod)_2$) and tris-(*o*-methoxyphenyl)-phosphine and triphenylphosphine were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere and used without further purification. Ethylene was purchased from BOC Gases and used as received. 1-octene was purchased from Alfa Aesar and used as received. All other alkenes were purchased from Aldrich Chemical Co. and used as received. Dicyclohexylphenylphosphine and ethyldiphenylphosphinite were purchased from Aldrich Chemical Co., stored under nitrogen atmosphere and used without further purification. Triethylsilyl trifluoromethanesulfonate (TESOTf) and trimethylsilyl trifluoromethansulfonate (TMSOTf) were purchased from Aldrich Chemical Co. and were distilled over calcium hydride before use. *tert*-Butyldimethysilyl trifluoromethanesulfonate (TBSOTf) was purchased from Alfa Aesar and was distilled over calcium hydride before use.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometers in $CDCl_3$ or C_6D_6, unless otherwise noted. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was

performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns.

Preparation of 2,2-dimethyl-3-oxo-propionic acid methyl ester



3-Hydroxy-2,2-dimethyl-propionic acid methyl ester (15 g, 113 mmol) in 200 mL dichloromethane was cooled to 0 °C. Pyridinium chlorochromate (43 g, 200 mmol) was added. The mixture was slowly warmed to room temperature and stirred 24 h. The crude in dichloromethane was filtered through silica gel. Celite was added to the remaining black viscous oil from the reaction mixture until the viscous oil is all absorbed to the celite. Dichloromethane was added to this slurry and the dichloromethane solution was filtered through silica gel. Dichloromethane was removed at reduced pressure (80 Torr) to give a pale yellow crude oil. Fractional distillation removed residue dichloromethane and obtained 2,2-dimethyl-3-oxo-propionic acid methyl ester as a colorless oil (7 g, 48% yield).

^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.60 (s, 1H); 3.70 (s, 3H); 1.29 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$, δ): 199.1, 173.2, 53.9, 52.6, 19.7.
IR (NaCl, thin film): 2988, 2958, 1726, 1468, 1278, 1151, 866.

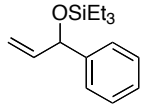
*Nickel-catalyzed couplings of ethylene and aldehydes (**1a, 1b, 1c, 1d, 1i, 1j, 1l, 1m, 1n**).*

General procedure 1. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 20 mol%) and tris-*o*-methoxyphenylphosphine (70.5 mg, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 15 min at room temperature. The reaction mixture was purged with ethylene for 1 min to remove argon, taken care not to introduce oxygen. The ethylene atmosphere was maintained with an ethylene balloon. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. Aldehyde (0.5 mmol, 100 mol%, as specified) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 3-18 h, as judged by the TLC of the reaction mixture. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification

via flash chromatography on silica afforded the coupling product.

*Nickel-catalyzed couplings of ethylene and aldehydes (**1e, 1f, 1g, 1h, 1k**).*

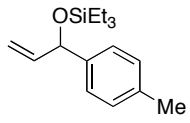
General procedure 2. A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 20 mol%), tris-*o*-methoxyphenylphosphine (70.5 mg, 0.2 mmol, 40 mol%) and aldehyde (0.5 mmol, 100 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 15 min at room temperature. The reaction mixture was purged with ethylene for 1 min to remove argon, taken care not to introduce oxygen. The ethylene atmosphere was maintained with an ethylene balloon. Next triethylamine (418 μL, 3 mmol, 600 mol%) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 3-18 h, as judged by TLC of the reaction mixture. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the coupling product.



1a

The reaction of ethylene and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1a** in 82% isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.32-7.45 (m, 4H); 7.29 (t, *J* = 7.0 Hz, 1H); 6.01 (ddd, *J* = 6.0, 10.2, 16.9 Hz, 1H); 5.34 (dt, *J* = 1.5, 16.9 Hz, 1H); 5.25 (d, *J* = 5.9 Hz, 1H); 5.13 (dt, *J* = 1.5, 10.2 Hz, 1H); 0.99 (t, *J* = 8.0 Hz, 9H); 0.66 (dq, *J* = 1.8, 7.8 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 143.9, 141.8, 128.4, 127.3, 126.2, 113.7, 75.9, 7.0, 5.1.
IR (NaCl, thin film): 2956, 2877, 1640, 1454, 1240, 1065, 744, 699.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{24}OSiNa$, 271.1489; found, 271.1499.



1b

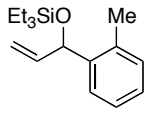
The reaction of ethylene and *p*-tolualdehyde (59 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1b** in 88% isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.27 (d, *J* = 8.0, 2H); 7.16 (d, *J* = 8.0 Hz, 2H); 5.97 (ddd, *J* = 5.9, 10.2, 16.9 Hz, 1H); 5.30 (dt, *J* = 1.5, 17.0 Hz, 1H); 5.17 (d, *J* = 5.9 Hz, 1H); 5.09 (dt, *J* = 1.3, 10.2 Hz, 1H); 2.37 (s, 3H); 0.97 (t, *J* = 7.9 Hz, 9H); 0.65 (dq, *J* = 1.9, 7.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.1, 141.1, 136.8, 129.1, 126.2, 113.4, 75.8, 21.3, 7.0, 5.2.

IR (NaCl, thin film): 2955, 2877, 1640, 1513, 1458, 1415, 1079, 1007, 844.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{26}OSiNa$, 285.1645; found, 285.1652.



1c

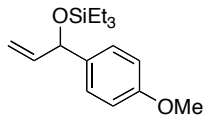
The reaction of ethylene and *o*-tolualdehyde (58 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1c** in 93% isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50 (d, *J* = 7.0, 1H); 7.11-7.24 (m, 3H); 5.93 (ddd, *J* = 5.7, 10.2, 17.0 Hz, 1H); 5.36 (d, *J* = 5.6 Hz, 1H); 5.22 (dt, *J* = 1.6, 17.1 Hz, 1H); 5.08 (dt, *J* = 1.5, 10.2 Hz, 1H); 2.34 (s, 3H); 0.95 (t, *J* = 8.0 Hz, 9H); 0.61 (dq, *J* = 2.8, 7.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 141.9, 140.7, 134.4, 130.3, 127.1, 126.5, 126.3, 113.7, 73.1, 19.4, 7.0, 5.1.

IR (NaCl, thin film): 2955, 2877, 1639, 1461, 1066, 1007, 744.

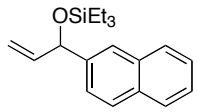
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{26}OSiNa$, 285.1645; found, 285.1649.



1d

The reaction of ethylene and *p*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1d** in 95% isolated yield as a colorless oil.

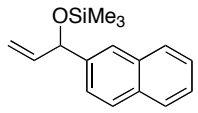
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (d, *J* = 8.7 Hz, 2H); 6.90 (d, *J* = 8.7 Hz, 2H); 5.97 (ddd, *J* = 5.9, 10.2, 16.9 Hz, 1H); 5.29 (dt, *J* = 1.4, 17.0 Hz, 1H); 5.16 (d, *J* = 5.9 Hz, 1H); 5.10 (dt, *J* = 1.4, 10.2 Hz, 1H); 3.83 (s, 3H); 0.96 (t, *J* = 7.9 Hz, 9H); 0.63 (dq, *J* = 1.8, 7.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.9, 142.0, 136.2, 127.4, 113.7, 113.4, 75.4, 55.4, 7.0, 5.1.
IR (NaCl, thin film): 2955, 2877, 1639, 1511, 1464, 1246, 1037, 744.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{26}O_2SiNa$, 301.1600; found, 301.1586.



1e

The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1e** in 95% isolated yield as a colorless oil.

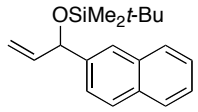
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.82-7.92 (m, 4H); 7.48-7.55 (m, 3H); 6.07 (ddd, *J* = 6.2, 10.2, 15.8 Hz, 1H); 5.35-5.45 (m, 2H); 5.17 (dt, *J* = 1.3, 10.1 Hz, 1H); 1.00 (t, *J* = 7.8 Hz, 9H); 0.68 (dq, *J* = 2.5, 7.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 141.7, 141.4, 133.5, 133.0, 128.2, 128.1, 127.7, 126.1, 125.8, 124.8, 124.6, 114.0, 76.0, 7.0, 5.1.
IR (NaCl, thin film): 2955, 2876, 1640, 1458, 1239, 1006, 743.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{26}OSiNa$, 321.1651; found, 321.1642.



1f

The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TMSOTf (158 μL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1f** in 60% isolated yield as a colorless oil.

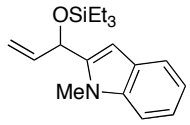
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.80-7.90 (m, 4H); 7.45-7.54 (m, 3H); 6.06 (ddd, *J* = 5.6, 10.2, 17.4 Hz, 1H); 5.30 (dt, *J* = 1.5, 17.3 Hz, 1H); 5.37 (bs, 1H); 5.17 (dt, *J* = 1.4, 10.2 Hz, 1H); 0.18 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 141.4, 141.0, 133.5, 133.0, 128.19, 128.18, 127.9, 126.2, 125.9, 124.9, 124.8, 114.4, 76.1, 0.4.
IR (NaCl, thin film): 2958, 1640, 1251, 1077, 841.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{20}OSiNa$, 279.1176; found, 279.1187.



1g

The reaction of ethylene and 2-naphthaldehyde (78.1 mg, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TBSOTf (201 μL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1g** in 67% isolated yield as a colorless oil.

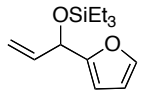
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.80-7.92 (m, 4H); 7.45-7.55 (m, 3H); 6.04 (ddd, *J* = 5.8, 10.2, 16.8 Hz, 1H); 5.39 (dt, *J* = 1.5, 17.0 Hz, 1H); 5.38 (s, 1H); 5.14 (dt, *J* = 1.5, 10.2 Hz, 1H); 0.99 (s, 9H); 0.16 (s, 3H); 0.06 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 141.8, 141.4, 133.5, 133.0, 128.2, 128.1, 127.9, 126.1, 125.8, 124.8, 124.6, 113.8, 76.2, 26.1, 18.6, -4.4, -4.6.
IR (NaCl, thin film): 2956, 2857, 1636, 1472, 1252, 1081, 837.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{26}OSiNa$, 321.1651; found, 321.1643.



1h

The reaction of ethylene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1h** in 67% isolated yield as a colorless oil.

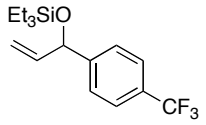
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63 (d, *J* = 7.8 Hz, 1H); 7.36 (d, *J* = 8.2 Hz, 1H); 7.26 (t, *J* = 8.3 Hz, 1H); 7.14 (t, *J* = 7.9 Hz, 1H); 6.43 (s, 1H); 6.13 (ddd, *J* = 4.5, 10.3, 17.1 Hz, 1H); 5.52 (ddd, *J* = 1.7, 1.7, 4.5 Hz , 1H); 5.39 (ddd, *J* = 1.7, 1.7, 17.1 Hz, 1H); 5.25 (ddd, *J* = 1.7, 1.7, 10.4, 1H); 3.82 (s, 3H); 0.98 (t, *J* = 8.0 Hz, 9H); 0.66 (dq, *J* = 1.4, 8.0 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 140.6, 139.7, 138.5, 127.5, 121.5, 120.8, 119.4, 114.9, 109.1, 100.5, 70.4, 31.0, 7.0, 5.0.
IR (NaCl, thin film): 2955, 2911, 2876, 1911, 1758, 1641, 1469, 1238, 1009, 841, 731.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{18}H_{28}NOSiNa$, 302.1935; found, 302.1944.



1i

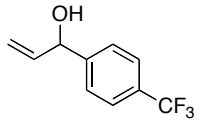
The reaction of ethylene and furan-2-carbaldehyde (41 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1i** in 38% isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.37 (bs, 1H); 6.32 (dd, *J* = 1.9, 3.1 Hz, 1H); 6.22 (d, *J* = 3.2 Hz, 1H); 6.06 (m, 1H); 5.40 (d, *J* = 17.1 Hz, 1H); 5.21 (d, *J* = 7.9 Hz, 2H); 0.95 (t, *J* = 7.9 Hz, 9H); 0.63 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.0, 142.1, 138.1, 115.3, 110.4, 106.4. 69.3, 6.9, 4.9.
IR (NaCl, thin film): 2956, 2878, 1646, 1459, 1237, 1010, 733.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{13}H_{22}O_2SiNa$, 261.1287; found, 261.1285.



1j

The reaction of ethylene and 4-(trifluoromethyl)-benzaldehyde (70 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded a mixture of **1j** and triethylsilylethers of pinnacol coupling products. This mixture was subjected to TBAF to isolate 25% of the desilylated **1j** as a colorless oil.



desilylated **1j**

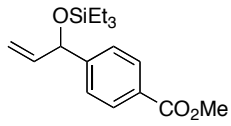
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.62 (d, *J* = 8.2 Hz, 2H); 7.50 (d, *J* = 8.4 Hz, 2H); 6.02 (ddd, *J* = 6.3, 10.3, 16.9 Hz, 1H); 5.38 (ddd, *J* = 1.2, 1.2, 17.0 Hz, 1H); 5.27 (bd, *J* = 7.0 Hz, 1H); 5.25 (ddd, *J* = 1.2, 1.2, 10.3 Hz, 1H); 2.10 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 146.5, 139.8, 130.0 (*J* = 32.3 Hz), 126.7, 125.7, 123.0, 116.4, 75.1.

^{19}F NMR (376 MHz, $CDCl_3$, δ): -66.8 (s, 3F).

IR (NaCl, thin film): 3342, 1620, 1419, 1328, 1166, 1126, 1068, 931.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{10}H_9OF_3SiNa$, 202.0600; found, 202.0591.



1k

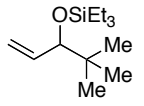
The reaction of ethylene and methyl-4-formyl-benzoate (88 mg, 0.536 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 2 above, afforded **1k** in 34% isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.01 (d, *J* = 8.4 Hz, 2H); 7.43 (d, *J* = 8.1 Hz, 2H); 5.92 (ddd, *J* = 6.0, 10.2, 16.9 Hz, 1H); 5.31 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H); 5.21 (bd, *J* = 6.0 Hz, 1H); 5.11 (ddd, *J* = 1.4, 1.4, 10.2 Hz, 1H); 3.91 (s, 3H); 0.93 (t, *J* = 7.8 Hz, 9H); 0.61 (dq, *J* = 1.7, 7.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.2, 149.1, 141.1, 129.8, 129.1, 126.1, 114.5, 75.6, 52.2, 6.9, 5.0.

IR (NaCl, thin film): 2954, 2912, 2877, 1727, 1610, 1436, 1278, 1113, 1019, 842, 745.

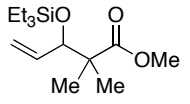
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{26}O_3SiNa$, 329.1543; found, 329.1548.



1l

The reaction of ethylene and pivaldehyde (55 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1l** in 70% isolated yield as a colorless oil.

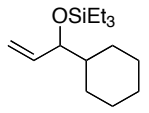
^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.97 (ddd, *J* = 5.9, 10.2, 16.9 Hz, 1H); 5.11 (d, *J* = 8.5 Hz, 1H); 5.08 (bs, 1H); 3.67 (d, *J* = 7.5 Hz, 1H); 0.96 (t, *J* = 7.9 Hz, 9H); 0.86 (s, 9H); 0.63 (q, *J* = 7.7 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 139.4, 115.8, 82.4, 35.5, 26.0, 7.2, 5.3.
IR (NaCl, thin film): 2955, 2877, 1641, 1462, 1239, 1082, 835.



1m

The reaction of ethylene and 2,2-dimethyl-3-oxo-propionic acid methyl ester (70 mg, 0.54 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1m** in 81% (0.28 mmol) isolated yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.75 (ddd, *J* = 7.6, 10.4, 17.5 Hz, 1H); 5.17 (bd, *J* = 17.3 Hz, 1H); 5.15 (bd, *J* = 10.3 Hz, 1H); 4.31 (d, *J* = 7.6 Hz, 1H); 3.66 (s, 3H); 1.15 (s, 3H); 1.05 (s, 3H); 0.92 (t, *J* = 7.9 Hz, 9H); 0.55 (dq, *J* = 1.5, 7.6 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 177.4, 137.8, 117.3, 79.2, 51.8, 48.3, 21.4, 19.9, 7.0, 5.2.
IR (NaCl, thin film): 2954, 2878, 1745, 1732, 1642, 1468, 1261, 1087, 834.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{14}H_{28}O_3SiNa$, 295.1700; found, 295.1714.



1n

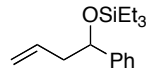
The reaction of ethylene and cyclohexanecarboxaldehyde (60 μL, 0.5 mmol) with $Ni(cod)_2$, tris-*o*-methoxy-phenylphosphine and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 1 above, afforded **1n** in 25% yield as determined by ^1H NMR versus a standard. Another experiment was carried out under 2 atm of ethylene and yielded 34% **1n** and 66% silyl enol ether of cyclohexanecarboxaldehyde. Treatment of this mixture with a TBAF / THF / H_2O solution removed the silyl enol ether from the mixture and column chromatography isolated **1n** as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$, δ): 5.78 (ddd, J = 7.0, 10.3, 17.3 Hz, 1H); 5.07 (m, 2H); 3.78 (t, J = 6.6 Hz, 1H); 1.40-0.90 (m, 11H); 0.95 (t, J = 8.0 Hz, 9H); 0.59 (q, J = 8.0 Hz, 6H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 140.7, 114.8, 78.9, 44.5, 29.0, 29.0, 26.9, 26.5, 26.5, 7.1, 5.2.
IR (NaCl, thin film): 2953, 2926, 2877, 1644, 1451, 1239, 1068, 743.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{30}OSiNa$, 277.1958; found, 277.1968.

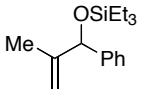
Nickel-catalyzed coupling of monosubstituted olefins and aldehydes (2a – 2p).

Nickel-catalyzed coupling of monosubstituted alkenes and aldehydes (homoallylic products)

General procedure 3. A 10 mL test tube and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 20 mol%) and ligand (0.2 mmol, 40 mol% as specified) were added to the test tube, the test tube was sealed with a septum, and the sealed tube was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. Alkene (0.5 mL), triethylamine (418 μL, 3 mmol, 600 mol%) and then aldehyde (0.5 mmol, 100 mol%) were added. TESOTf (197 μL, 0.875 mmol, 175 mol%) was added. The mixture was stirred at room temperature for 48 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the coupling product.

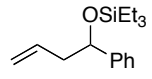


2a



2a'

A 10 mL test tube and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 20 mol%) and $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. The reaction mixture was purged with propene for 1 min to remove argon, taken care not to introduce oxygen. The propene atmosphere was maintained with a propene balloon. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. benzaldehyde (51 μL, 0.5 mmol, 100 mol%) was added. Silyl triflate (0.875 mmol, 175 mol%, as specified) was added. The mixture was stirred at room temperature for 48 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and ^{1}H NMR of the crude mixture indicated the total yield of **2a** and **2a'** was 73% and the ratio of **2a**:**2a'** is 89:11. Purification via flash chromatography on silica afforded **2a** and **2a'** as colorless oils.



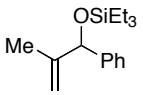
2a

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.27-7.38 (m, 5H); 5.78-5.89 (m, 1H); 5.05-5.10 (m, 2H); 4.74 (dd, *J* = 7.2, 5.5 Hz, 1H); 2.42-2.59 (m, 2H); 0.94 (t, *J* = 7.9 Hz, 9H); 0.59 (dq, *J* = 2.6, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.3, 135.4, 128.2, 127.2, 126.1, 117.0, 75.1, 45.6, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2927, 2876, 1644, 1493, 1449, 1239, 1090, 858, 699.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{26}OSiNa$, 285.1645; found, 285.1633.



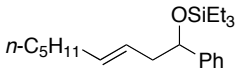
2a'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.24-7.39 (m, 5H); 5.15 (m, 2H); 4.86 (s, 1H); 1.56 (s, 3H); 0.94 (t, *J* = 7.8 Hz, 9H); 0.61 (q, *J* = 7.8 Hz, 6H).

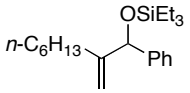
^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.1, 143.5, 128.1, 127.0, 126.3, 111.0, 78.4, 17.4, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2913, 2877, 1451, 1237, 1091, 1066, 1005, 899, 853, 740, 698.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{26}OSiNa$, 285.1645; found, 285.1651.



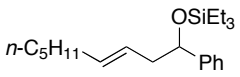
2b



2b'

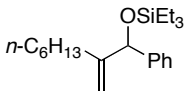
The reaction of 1-octene and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2b** and **2b'** in 85% total yield according to ^1H NMR of the crude mixture and the ratio of **2b**:**2b'** is 95:5. The *E* / *Z* ratio of **2b** is 75:25. Purification via flash chromatography on silica afforded **2b** and **2b'** as colorless oils.

In another experiment, the reaction of 1-octene (1 mL) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, Cy_2PhP (56 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2b'** and **2b** in 73% total yield according to ^1H NMR of the crude mixture and the ratio of **2b'**:**2b** is 71:29. Purification via flash chromatography on silica afforded **2b'** and **2b** in 70% isolated yield as a colorless oil.



2b

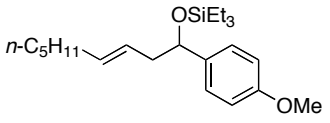
^1H NMR (400 MHz, $CDCl_3$, δ): 7.20-7.40 (m, 5H); 5.30-5.50 (m, 2H); 4.63 (dd, *J* = 5.6, 7.2 Hz, 1H); 2.45 (quintet, *J* = 6.1 Hz, 1H); 2.35 (quintet, *J* = 5.9 Hz, 1H); 1.33 (m, 2H); 0.92 (t, *J* = 7.8 Hz, 12H); 0.56 (dq, *J* = 2.4, 7.6 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.6, 133.3, 128.1, 127.1, 126.6, 126.2, 75.6, 44.5, 32.8, 31.6, 29.3, 22.8, 14.2, 7.0, 5.1.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{36}OSiNa$, 355.2428; found, 355.2437.



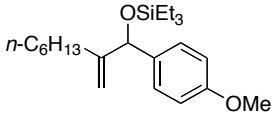
2b'

^1H NMR (400 MHz, $CDCl_3$, δ): 7.36 (d, *J* = 7.0 Hz, 2H); 7.31 (t, *J* = 7.1 Hz, 2H); 7.24 (t, *J* = 7.2, 1H); 5.22 (bs, 1H); 5.15 (bs, 1H); 4.87 (s, 1H); 1.96 (pentet, *J* = 7.8 Hz, 1H); 1.76 (pentet, *J* = 8.0 Hz, 1H); 1.15-1.40 (m, 8H); 0.93 (t, *J* = 8.0 Hz, 9H); 0.87 (t, *J* = 6.8 Hz, 3H); 0.60 (dq, *J* = 1.6, 7.9 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.3, 143.8, 128.1, 127.1, 126.6, 109.5, 78.3, 32.0, 30.8, 29.4,

28.0, 22.8, 14.3, 7.0, 5.1.
IR (NaCl, thin film): 2956, 2876, 1647, 1456, 1089, 1066, 742.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{36}OSiNa$, 355.2428; found, 355.2419.

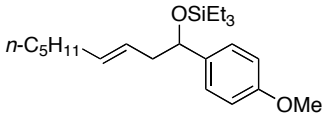


2c



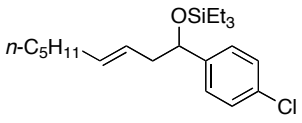
2c'

The reaction of 1-octene and 4-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2c** and **2c'** in 85% total yield according to ^1H NMR of the crude mixture and the ratio of **2c**:**2c'** is > 95:5. The *E* / *Z* ratio of **2c** is 75:25. Purification via flash chromatography on silica afforded **2c** as a colorless oil. **2c'** was not detected.

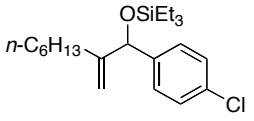


2c

^1H NMR (400 MHz, $CDCl_3$, δ): 7.22 (d, *J* = 8.6 Hz, 2H); 6.84 (d, *J* = 8.6 Hz, 2H); 5.33-5.43 (m, 2H); 4.58 (dd, *J* = 6.1 Hz, 6.1 Hz, 1H); 3.81 (s, 3H); 2.27-2.42 (m, 2H); 1.93-1.98 (m, 2H); 1.22-1.60 (m, 6H); 0.95 (t, *J* = 8.0 Hz, 3H); 0.88 (t, *J* = 7.8 Hz, 9H); 0.53 (q, *J* = 7.8 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.7, 137.9, 133.2, 127.3, 126.7, 113.4, 75.2, 55.4, 44.5, 32.8, 31.6, 29.3, 22.8, 14.3, 7.0, 5.0.
IR (NaCl, thin film): 2955, 2876, 1613, 1512, 1459, 1302, 1247, 1172, 1078, 1005, 972, 830, 742.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{38}O_2SiNa$, 385.2539; found, 385.2537.

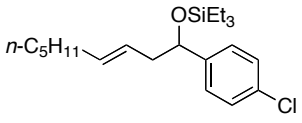


2d



2d'

The reaction of 1-octene and 4-chlorobenzaldehyde (70 mg, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2d** and **2d'** in 37% total yield according to ^1H NMR of the crude mixture and the ratio of **2d**:**2d'** is > 95:5. The *E* / *Z* ratio of **2d** is 74:26. Purification via flash chromatography on silica afforded **2d** as a colorless oil. **2d'** was not detected.



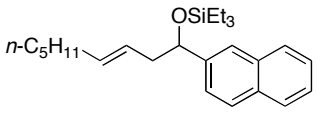
2d

^1H NMR (400 MHz, $CDCl_3$, δ): 7.24 (m, 4H); 5.30-5.41 (m, 2H); 4.61 (dd, *J* = 6.1 Hz, 6.1 Hz, 1H); 2.26-2.40 (m, 2H); 1.89-1.97 (m, 2H); 1.21-1.59 (m, 6H); 0.94 (t, *J* = 8.0 Hz, 3H); 0.89 (t, *J* = 7.8 Hz, 9H); 0.54 (q, *J* = 7.8 Hz, 6H).

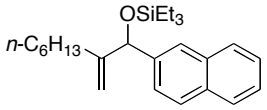
^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.1, 133.7, 132.5, 128.2, 127.5, 126.0, 74.8, 44.4, 32.8, 31.5, 29.2, 22.7, 14.3, 7.0, 4.9.

IR (NaCl, thin film): 2956, 2876, 1647, 1456, 1089, 1066, 742.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{20}Na$, 223.1463; found, 223.1305.

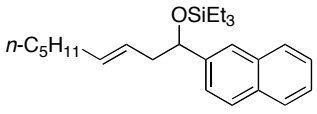


2e



2e'

The reaction of 1-octene and 2-naphthaldehyde (78 mg, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2e** and **2e'** in 88% total yield according to ^1H NMR of the crude mixture and the ratio of **2e**:**2e'** is > 95:5. The *E* / *Z* ratio of **2e** is 70:30. Purification via flash chromatography on silica afforded **2e** as a colorless oil. **2e'** was not detected.



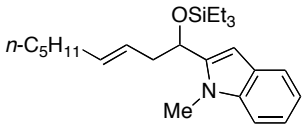
2e

^1H NMR (400 MHz, $CDCl_3$, δ): 7.83-7.92 (m, 3H); 7.80 (s, 1H); 7.48-7.59 (m, 3H); 5.43-5.53 (m, 2H); 4.89 (dd, *J* = 6.9, 13.2 Hz, 1H); 2.45-2.68 (m, 2H); 1.98-2.05 (m, 2H); 1.26-1.39 (m, 6H); 0.97 (t, *J* = 8.0 Hz, 9H); 0.94 (t, *J* = 7.6 Hz, 3H); 0.63 (q, *J* = 4.1, 8.0 Hz 6H).

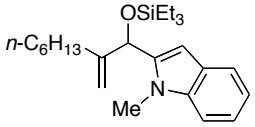
^{13}C NMR (100 MHz, $CDCl_3$, δ): 143.1, 133.4, 133.0, 132.3, 128.1, 127.9, 126.5, 126.0, 125.6, 125.6, 124.7, 124.7, 75.7, 44.4, 32.8, 31.7, 29.3, 22.8, 14.3, 7.0, 5.1.

IR (NaCl, thin film): 2956, 2929, 2875, 1458, 1414, 1377, 1239, 1086, 1005, 972, 744.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{25}H_{38}OSiNa$, 405.2590; found, 405.2584.

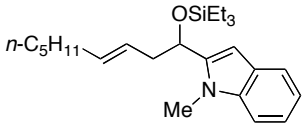


(2f)



2f'

The reaction of 1-octene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2f** and **2f'** in 56% total yield according to ^1H NMR of the crude mixture and the ratio of **2f**:**2f'** is > 95:5. The *E* / *Z* ratio of **2f** is 83:17. Purification via flash chromatography on silica afforded **2f** as a colorless oil. **2f'** was not detected.



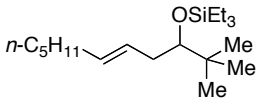
2f

^1H NMR (400 MHz, $CDCl_3$, δ): 7.65 (d, *J* = 7.8 Hz, 1H); 7.37 (d, *J* = 8.2 Hz, 1H); 7.27 (t, *J* = 7.1 Hz, 1H); 7.17 (t, *J* = 7.1 Hz, 1H); 6.40 (s, 1H); 5.43-5.59 (m, 2H); 4.96 (dd, *J* = 6.5, 7.4 Hz, 1H); 3.92 (s, 3H); 2.56-2.71 (m, 2H); 2.01-2.07 (m, 2H); 1.29-1.42 (m, 6H); 0.97 (t, *J* = 8.0 Hz, 9H); 0.95 (t, *J* = 4.0 Hz, 3H); 0.63 (dq, *J* = 1.1, 8.0 Hz, 6H).

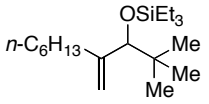
^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.3, 138.4, 133.7, 127.7, 126.2, 121.3, 120.7, 119.4, 109.1, 100.2, 70.6, 42.2, 32.8, 31.6, 31.0, 29.3, 22.8, 14.3, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2927, 2874, 1466, 1339, 1236, 1072, 1010, 731.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{24}H_{39}ONSiNa$, 408.2693; found, 408.2695.

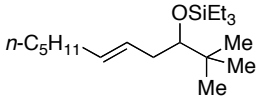


2g



2g'

The reaction of 1-octene and pivaldehyde (55 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2g** and **2g'** in 64% total yield according to ^1H NMR of the crude mixture and the ratio of **2g**:**2g'** is > 95:5. The *E* / *Z* ratio of **2g** is 78:22. Purification via flash chromatography on silica afforded **2g**. **2g'** was not detected.



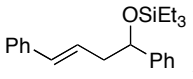
2g

^1H NMR (400 MHz, $CDCl_3$, δ): 5.37-5.53 (m, 2H); 3.37 (dd, *J* = 3.8, 7.4 Hz, 1H); 2.30-2.36 (m, 1H); 1.99-2.12 (m, 3H); 1.27-1.42 (m, 6H); 0.99 (t, *J* = 8.0 Hz, 9H); 0.92 (t, *J* = 6.8 Hz, 3H); 0.90 (s, 9H); 0.63 (q, *J* = 8.0 Hz, 6H).

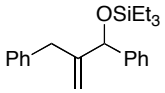
^{13}C NMR (100 MHz, $CDCl_3$, δ): 130.6, 128.5, 81.2, 36.2, 31.8, 31.4, 29.5, 27.6, 26.5, 22.8, 14.2, 7.3, 5.7.

IR (NaCl, thin film): 2956, 2876, 1466, 1238, 1096, 1009, 737.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{40}OSiNa$, 335.2746; found, 335.2741.

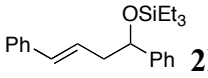


2h



2h'

The reaction of allylbenzene and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2h** and **2h'** in 86% total yield according to ^1H NMR of the crude mixture and the ratio of **2h**:**2h'** is 92:8. The *E* / *Z* ratio of **2h** is > 95:5. Purification via flash chromatography on silica afforded **2h** as a colorless oil. **2h'** was subjected to TBAF and the free alcohol was isolated by flash chromatography on silica as a colorless oil.



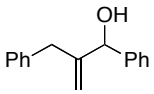
2h

^1H NMR (400 MHz, $CDCl_3$, δ): 7.30-7.50 (m, 10H); 6.51 (d, *J* = 15.9 Hz, 1H); 6.34 (dt, *J* = 7.2, 15.9 Hz, 1H); 4.89 (dd, *J* = 5.3, 7.2 Hz, 1H); 2.64-2.81 (m, 2H); 1.03 (t, *J* = 7.9 Hz, 9H); 0.68 (dq, *J* = 2.0, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.5, 138.0, 132.4, 128.8, 128.4, 127.4, 127.4, 127.2, 126.3, 126.2, 75.5, 45.0, 7.1, 5.2.

IR (NaCl, thin film): 3062, 3028, 2955, 2911, 2876, 1600, 1494, 1453, 1414, 1239, 1088, 1070, 1006, 965, 830, 742, 700.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for 361.1964; found, 361.1974.



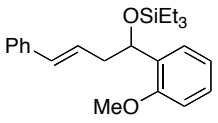
desilylated **2h'**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.39 (m, 4H), 7.29-7.35 (m, 3H), 7.22-7.24 (m, 1H), 7.13-7.15 (m, 2H), 5.37 (s, 1H); 5.15 (s, 1H); 4.93 (s, 1H); 3.38 (d, *J* = 15.5 Hz, 1H); 3.13 (d, *J* = 15.5 Hz, 1H); 1.24 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.6, 142.0, 139.3, 129.4, 128.7, 128.5, 128.1, 127.0, 126.4, 112.4, 76.7, 39.2.

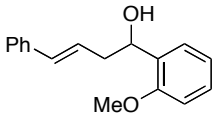
IR (NaCl, thin film): 3377, 3061, 3028, 2919, 1494, 1453, 1025, 909, 750, 699.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{16}H_{16}ONa$, 247.1099; found, 247.1101.



2i-ortho

The reaction of allylbenzene and *o*-anisaldehyde (60 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2i-ortho** and **2i'-ortho** in 78% total yield according to ^1H NMR of the crude mixture and the ratio of **2i-ortho**:**2i'-ortho** is 92:8. The *E* / *Z* ratio of **2i-ortho** is > 95:5. **2i-ortho** was subjected to TBAF and the free alcohol was isolated as a colorless oil. Allylic alcohol **2i'-ortho** was not isolated.



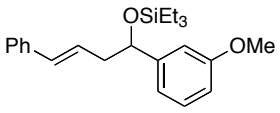
desilylated **2i-ortho**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.22-7.43 (m, 7H); 7.02 (t, *J* = 7.5 Hz, 1H); 6.93 (d, *J* = 8.1 Hz, 1H); 6,52 (d, *J* = 15.9 Hz, 1H); 6.31 (dt, *J* = 7.2, 15.9 Hz, 1H); 5.09 (dd, *J* = 5.1, 7.5 Hz, 1H); 3.89 (s, 3H); 2.69-2.81 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.5, 137.6, 132.8, 131.9, 128.6, 128.5, 127.3, 127.0, 126.9, 126.3, 120.9, 110.6, 70.2, 55.5, 41.3.

IR (NaCl, thin film): 3399, 3026, 2935, 2836, 1601, 1491, 1464, 1438, 1287, 1240, 1181, 1049, 1029, 966, 753, 694.

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{32}O_2SiNa$, 391.2069; found, 391.2053.



2i-meta

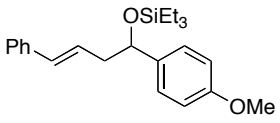
The reaction of allylbenzene and *m*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2i-meta** and **2i'-meta** in 96% total yield according to ^1H NMR of the crude mixture and the ratio of **2i-meta**:**2i'-meta** is 92:8. The *E* / *Z* ratio of **2i-meta** is > 95:5. Purification via flash chromatography on silica afforded **2i-meta** as a colorless oil. Allylic alcohol **2i'-meta** was not isolated.

^1H NMR (400 MHz, $CDCl_3$, δ): 7.25-7.41 (m, 6H), 7.03 (m, 1H), 7.0 (d, *J* = 7.6 Hz, 1H); 6.87 (dd, *J* = 0.8, 2.7 Hz, 1H); 6.48 (d, *J* = 15.9 Hz, 1H); 6.30 (dt, *J* = 7.2, 15.9 Hz, 1H); 3.87 (s, 3H); 2.61-2.75 (m, 2H), 0.99 (t, *J* = 7.9 Hz, 9H); 0.64 (q, *J* = 7.9 Hz, 6H).

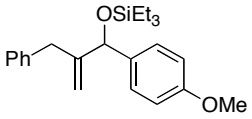
^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.7, 147.1, 137.9, 134.0, 133.8, 132.3, 129.2, 128.9, 128.7, 128.6, 127.2, 127.1, 126.2, 118.4, 112.8, 111.3, 75.2, 55.3, 44.8, 7.0, 5.0.

IR (NaCl, thin film): 3027, 2954, 2910, 2876, 2835, 1601, 1587, 1488, 1456, 1435, 1359, 1320, 1284, 1263, 1153, 1083, 1050, 1006, 966, 943, 825, 779, 743, 699.

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{32}O_2SiNa$, 391.2069; found, 391.1750.



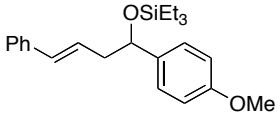
2i-para



2i'-para

The reaction of allylbenzene and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2i-para** and **2i'-para** in 99% total yield according to ^1H NMR of the crude mixture and the ratio of **2i-para**:**2i'-para** is 92:8. The *E* / *Z* ratio of **2i-para** is > 95:5. Purification via flash chromatography on silica afforded **2i-para** as a colorless oil. **2i'-para** was not isolated.

In another experiment, general procedure 3 was followed, except that the reaction was carried out in five fold larger scale. The reaction was heated at 35 °C and 9 mL toluene was used as the solvent. This reaction afforded **2i-para** and **2i'-para** in 98% total yield according to ^1H NMR of the crude mixture and the ratio of **2i-para**:**2i'-para** is 92:8. The *E* / *Z* ratio of **2i-para** is > 95:5. Purification via flash chromatography on silica afforded **2i-para** as a colorless oil. **2i'-para** was not isolated.



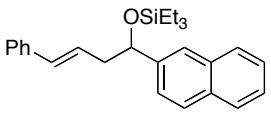
2i-para

^1H NMR (400 MHz, $CDCl_3$, δ): 7.49 (m, 7H); 7.00 (d, *J* = 8.6 Hz, 2H); 6.52 (d, *J* = 15.9 Hz, 1H); 6.35 (dt, *J* = 7.2, 15.9 Hz, 1H); 4.85 (dd, *J* = 6.4, 6.4 Hz, 1H); 3.89 (s, 3H); 2.63-2.81 (m, 2H); 1.04 (t, *J* = 7.8 Hz, 9H); 0.70 (q, *J* = 7.8 Hz, 6H).

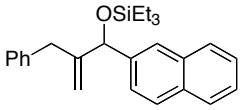
^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.0, 138.1, 137.7, 132.3, 128.7, 127.5, 127.3 127.2, 126.3, 113.7, 75.0, 55.4, 45.1, 7.1, 5.2.

IR (NaCl, thin film): 3027, 2954, 2910, 2875, 1612, 1511, 1414, 1302, 1248, 1171, 1081, 1005, 966, 836, 743, 693.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{32}O_2SiNa$, 391.2069; found, 391.2057.

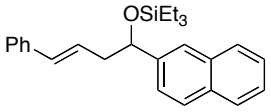


2j



2j'

The reaction of allylbenzene and naphthaldehyde (78 mg, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2j** and **2j'** in 88% total yield according to ^1H NMR of the crude mixture and the ratio of **2j**:**2j'** is 95:5. The *E* / *Z* ratio of **2j** is > 95:5. Purification via flash chromatography on silica afforded **2j** as a colorless oil. **2j'** was subjected to TBAF and the free alcohol was isolated by flash chromatography on silica as a colorless oil.



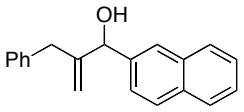
(2j)

^1H NMR (400 MHz, $CDCl_3$, δ): 7.90-7.96 (m, 4H); 7.67 (d, *J* = 1.6 Hz, 1H); 7.60-7.65 (m, 2H); 7.30-7.59 (m, 5H); 6.54 (d, *J* = 15.9 Hz, 1H); 6.36 (dt, *J* = 7.2, 15.9 Hz, 1H); 5.05 (dd, *J* = 5.4, 7.2 Hz, 1H); 2.74-2.89 (m, 2H); 1.03 (t, *J* = 8.0 Hz, 9H); 0.70 (dq, *J* = 2.9, 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.9, 137.9, 133.4, 133.1, 132.4, 128.7, 128.1, 128.1, 127.9, 127.1, 126.2, 126.1, 125.7, 124.6, 75.5, 44.9, 7.0, 5.1.

IR (NaCl, thin film): 3026, 2954, 2910, 2875, 1507, 1496, 1457, 1239, 1123, 1083, 1005, 965, 819, 744.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{26}H_{32}OSiNa$, 411.2120; found, 411.2167.



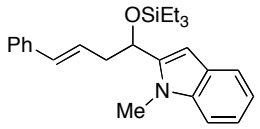
desilylated **2j'**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.86-7.88 (m, 4H); 7.48-7.55 (m, 3H); 7.20-7.36 (m, 3H); 7.13-7.16 (m, 2H); 5.43 (s, 1H); 5.32 (s, 1H); 4.97 (s, 1H); 3.41 (d, *J* = 15.6 Hz, 1H), 3.16 (d, *J* = 15.6 Hz, 1H), 2.02 (bs, 1H).

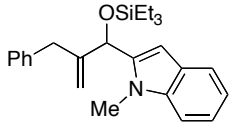
^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.5, 149.2, 139.4, 139.3, 133.4, 133.3, 129.4, 128.6, 128.2, 127.9, 126.4, 126.4, 126.2, 126.0, 124.9, 112.8, 77.4, 39.2.

IR (NaCl, thin film): 3365, 3058, 2923, 1495, 1453, 1031, 908, 819, 745, 700.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{18}ONa$, 297.1255; found, 297.1260.



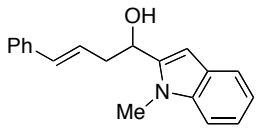
2k



2k'

The reaction of allylbenzene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2k** in 57% total yield according to ^1H NMR of the crude mixture and the ratio of **2k**:**2k'** is > 95:5. The *E* / *Z* ratio of **2k** is > 95:5. **2k'** was not detected. **2k** was subjected to TBAF and the free alcohols were isolated by flash chromatography on silica (buffered with Et_3N) as colorless oils.

In another experiment, the reaction of allylbenzene and 1-methyl-2-indolecarboxaldehyde (79.6 mg, 0.5 mmol) with $Ni(cod)_2$, Cy_2PhP (56mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2k'** and **2k** in 56% total yield according to ^1H NMR of the crude mixture and the ratio of **2k'**:**2k** is 80:20. The *E* / *Z* ratio of **2k** is > 95:5. Both **2k'** and **2k** were subjected to TBAF and the free alcohols were isolated by flash chromatography on silica (buffered with Et_3N) as colorless oils.



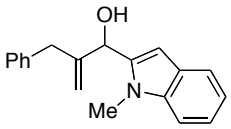
desilylated **2k**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.63 (d, *J* = 7.8 Hz, 1H); 7.20-7.41 (m, 7H); 7.14 (t, *J* = 7.8 Hz, 1H); 6.62 (d, *J* = 15.8 Hz, 1H); 6.55 (s, 1H); 6.34 (dt, *J* = 7.3, 15.8 Hz, 1H); 5.01 (m, 1H); 3.86 (s, 3H); 2.93-2.99 (m, 2H); 1.93 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 149.2, 141.3, 138.1, 137.2, 133.8, 128.7, 127.6, 126.4, 125.7, 122.1, 121.0, 119.8, 109.3, 99.4, 66.9, 40.2, 30.4.

IR (NaCl, thin film): 3640, 3026, 2953, 2910, 2875, 1467, 1339, 1237, 1073, 1006, 966, 744.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{19}ONNa$, 300.1364; found, 300.1365.



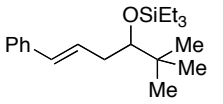
desilylated **2k'**

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63 (d, 1H); 7.12-7.38 (m, 8H); 6.49 (s, 1H); 5.38 (s, 1H); 5.31 (s, 1H); 5.14 (s, 1H); 3.70 (s, 3H); 3.54 (d, *J* = 15.3 Hz, 1H); 3.33 (d, *J* = 15.3 Hz, 1H); 1.98 (d, *J* = 5.1Hz, 1H).

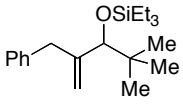
^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.7, 139.6, 139.1, 138.4, 129.3, 128.6, 127.3, 126.6, 122.0, 121.0, 119.7, 113.2, 109.3, 101.5, 69.6, 40.2, 30.3.

IR (NaCl, thin film): 3349, 3059, 3027, 2923, 1649, 1601, 1494, 1468, 1453, 1318, 1234, 1030, 968, 907, 751, 737, 700.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{19}NONa$, 300.1364; found, 300.1369.

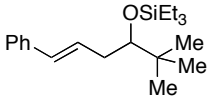


2l



2l'

The reaction of allylbenzene and pivaldehyde (55 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2l** in 65% total yield according to ^1H NMR of the crude mixture and the ratio of **2l**:**2l'** is > 95:5. The *E* / *Z* ratio of **2l** is 78:22. **2l'** was not detected. Purification via flash chromatography on silica afforded **2l** as a colorless oil.

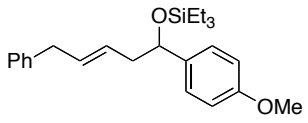


2l

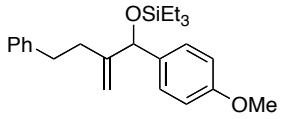
^1H NMR (400 MHz, $CDCl_3$, δ): 7.22-7.40 (m, 5H); 6.43 (d, *J* = 15.9 Hz, 1H); 6.32 (dt, *J* = 7.1, 15.9 Hz, 1H); 3.50 (dd, *J* = 3.4, 7.7 Hz, 1H); 2.49-2.55 (m, 1H), 2.28-2.35 (m, 1H), 1.00 (t, *J* = 8.0 Hz, 9H); 0.96 (s, 9H); 0.64 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 138.1, 131.3, 129.7, 128.7, 127.0, 126.1, 81.0, 37.4, 36.2, 26.6, 7.3, 5.7.

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{34}OSiNa$, 341.2277; found, 341.2263.

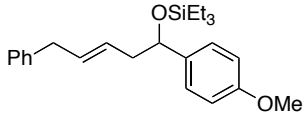


2m



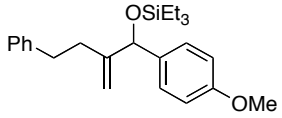
2m'

The reaction of 4-phenyl-1-butene and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2m** and **2m'** in 91% total yield according to ^1H NMR of the crude mixture and the ratio of **2m**:**2m'** is 92:8. The *E* / *Z* ratio of **2m** is 68:32. Purification via flash chromatography on silica afforded **2m** and **2m'** as colorless oils.



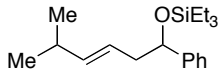
2m

^1H NMR (400 MHz, $CDCl_3$, δ): 7.13-7.42 (m, 7H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.49-5.69 (m, 2H), 4.76 (t, *J* = 6.3 Hz, 0.33 H), 4.70 (t, *J* = 6.4 Hz, 0.67 H), 3.87 (s, 3H), 3.37-3.39 (m, 2H), 2.35-2.81 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 6H); 0.60 (q, *J* = 7.9 Hz, 9H).

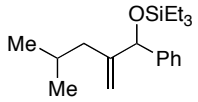


2m'

^1H NMR (400 MHz, $CDCl_3$, δ): 7.13-7.42 (m, 7H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 5.19 (s, 1H), 5.00 (s, 1H), 3.86 (s, 3H), 2.61-2.79 (m, 2H), 2.26-2.42 (m, 1H), 2.16-2.22 (m, 1H), 1.07 (t, *J* = 7.8 Hz, 9H); 0.74 (q, *J* = 7.9 Hz, 6H).



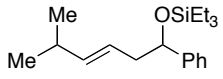
2n



2n'

The reaction of 4-methyl-1-pentene and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2n** and **2n'** in 82% total yield according to ^1H NMR of the crude mixture and the ratio of **2n**:**2n'** is > 95:5. The *E* / *Z* ratio of **2n** is 81:19. **2n'** was not detected. Purification via flash chromatography on silica afforded **2n** as a colorless oil.

In another experiment, a 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. 4-methyl-1-pentene (633 μL, 5 mmol, 1000 mol%) was added. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. Benzaldehyde (51 μL, 0.5 mmol, 100 mol%) was added to the reaction mixture, followed by TESOTf (197 μL, 0.875 mmol, 175 mol%). The mixture was stirred at room temperature for 14 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and NMR of the crude mixture indicated the ratio of **2n':2n** is 75:25. Purification via flash chromatography on silica afforded **2n'** in 44% isolated yield as a colorless oil and **2n** in 10% isolated yield.
This reaction can be run according to general procedure 3, which also afforded **2n'** and **2n** in similar yield.

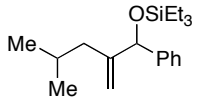


2n

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (m, *5*H); 5.40 (m, 2H); 4.63 (dd, *J* = 5.3, 7.3 Hz, 1H); 2.41 (quintet, *J* = 5.3 Hz, 1H); 2.30 (quintet, *J* = 5.5 Hz, 1H); 2.24 (septet, *J* = 6.7 Hz, 1H); 2.00 (m, 2H); 0.95 (dd, *J* = 6.7, 7.6 Hz, 6H); 0.89 (t, *J* = 7.9 Hz, 9H); 0.62 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.6, 140.2, 128.1, 127.0, 126.1, 123.7, 75.7, 44.5, 31.3, 22.6, 7.01, 5.0.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{32}OSiNa$, 327.2115; found, 327.2121.



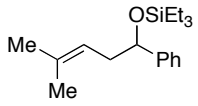
2n'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.36 (d, *J* = 7.8 Hz, 2H); 7.32 (t, *J* = 7.1 Hz, 2H); 7.25 (t, *J* = 7.1, 1H); 5.30 (bs, 1H); 5.12 (bs, 1H); 4.87 (bs, 1H); 1.65-1.85 (m, 3H); 0.93 (t, *J* = 8.0 Hz, 9H); 0.84 (d, *J* = 6.4 Hz, 3H); 0.82 (d, *J* = 6.2 Hz, 3H); 0.60 (dq, *J* = 1.3, 8.3 Hz, 6H).

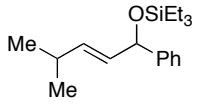
^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.5, 143.7, 128.1, 127.1, 126.7, 110.7, 77.9, 41.1, 26.3, 23.0, 22.6, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2877, 1646, 1454, 1088, 1067, 743.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{19}H_{32}OSiNa$, 327.2115; found, 327.2115.

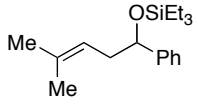


2o



2o'

The reaction of 3-methyl-1-butene and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2o** and **2o'** in 95% total yield according to ^1H NMR of the crude mixture and the ratio of **2o**:**2o'** is 86:14. The *E* / *Z* ratio of **2o'** is > 95:5. Purification via flash chromatography on silica afforded **2o**. **2o'** was not isolated.



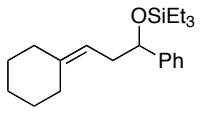
2o

^1H NMR (400 MHz, $CDCl_3$, δ): 7.27-7.43 (m, 5H); 5.19-5.24 (m, 1H); 4.68 (dd, *J* = 5.8, 7.2 Hz, 1H); 2.36-2.54 (m, 2H); 1.74 (d, *J* = 0.8 Hz, 3H); 1.58 (s, 3H); 0.95 (t, *J* = 7.8 Hz, 9H); 0.60 (dq, *J* = 3.4, 7.8 Hz, 6H).

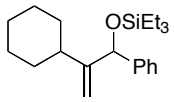
^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.8, 133.6, 128.1, 127.0, 126.1, 121.0, 75.4, 40.0, 26.0, 18.0, 7.0, 5.0.

IR (NaCl, thin film): 3028, 2956, 2877, 2912, 1454, 1414, 1377, 1239, 1089, 1069, 1005, 941, 744, 699.

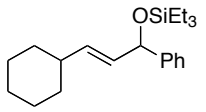
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{18}H_{30}OSiNa$, 313.1964; found, 313.1966.



2p



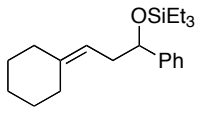
2p'



3p

The reaction of vinylcyclohexane and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **2p** and **3p** in 99% total yield according to ^1H NMR of the crude mixture and the ratio of **2p**:**3p** is 75:25. The *E* / *Z* ratio of **3p** is > 95:5. Purification via flash chromatography on silica afforded a mixture of **2p** and **3p**.

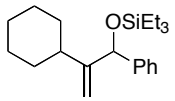
In another experiment, a 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. Vinylcyclohexane (856 μL, 6.25 mmol, 1250 mol%) was added. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. Benzaldehyde (51 μL, 0.5 mmol, 100 mol%) was added, followed by TESOTf (197 μL, 0.875 mmol, 175 mol%). The mixture was stirred at room temperature for 16 h. The mixture was filtered through a plug of silica gel. ^1H NMR of the crude mixture indicated that **2p'** is the minor product, along with homoallylic product **2p** and 1,3-disubstituted allylic product **3p** as major products. Purification via flash chromatography on silica afforded **2p'** in 5% isolated yield as a colorless oil.



2p

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.24-7.42 (m, 5H); 5.14 (t, *J* = 7.4 Hz, 1H); 4.66 (t, *J* = 6.4 Hz, 1H); 2.37-2.52 (m, 2H); 2.00-2.11 (m, 3H); 1.50-1.78 (m, 3H); 1.03-1.48 (m, 4H); 0.94 (t, *J* = 7.9 Hz, 9H); 0.59 (dq, *J* = 2.8, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.7, 141.6, 128.0, 127.0, 126.2, 117.5, 75.6, 39.0, 37.5, 29.0, 28.7, 27.8, 27.1, 7.0, 5.0.



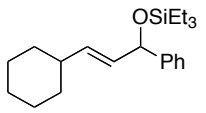
2p'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.33 (d, *J* = 8.6 Hz, 2H); 7.29 (t, *J* = 7.9, 2H); 7.22 (t, *J* = 7.0 Hz, 1H); 5.23 (dd, *J* = 1.3, 1.3 Hz, 1H); 5.14 (s, 1H); 4.90 (s, 1H); 1.2-2.0 (m, 11H); 0.91 (t, *J* = 7.9 Hz, 9H); 0.58 (dq, J = 0.5, 7.8 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.7, 143.7, 128.0, 127.1, 126.9, 108.2, 77.6, 39.5, 34.5, 33.5, 27.1, 27.0, 26.5, 7.1, 5.0.

IR (NaCl, thin film): 2954, 2927, 2876, 1644, 1493, 1449, 1239, 1090, 858, 699.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{34}OSiNa$, 353.2271; found, 353.2269.



3p

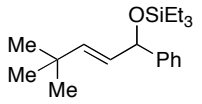
^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.24-7.42 (m, 5H); 5.69 (dd, *J* = 6.5, 15.4 Hz, 1H); 5.56 (dd, *J* = 7.0, 15.4 Hz, 1H); 5.18 (d, *J* = 7.0 Hz, 1H); 2.00-2.11 (m, 3H); 1.63-1.78 (m, 1H); 1.50-1.78 (m, 3H); 1.03-1.48 (m, 4H); 1.00 (t, *J* = 8.0 Hz, 9H); 0.67 (dq, *J* = 2.3, 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.8, 136.9, 131.2, 128.2, 126.9, 126.1, 75.9, 40.4, 33.0, 32.9, 26.4, 26.2, 7.1, 5.2.

The following IR and HRMS data is from a mixture of **2p** and **2p'**.

IR (NaCl, thin film): 2954, 2928, 2876, 2853, 1449, 1414, 1238, 1086, 1067, 1007, 969, 829, 744, 699.

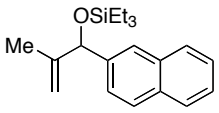
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{34}OSiNa$, 353.2277; found, 353.2267.



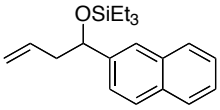
3q

The reaction of 3,3-dimethyl-1-butene and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **3q** only in 14% total yield according to ^1H NMR of the crude mixture. Purification via flash chromatography on silica afforded **3q** as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$, δ): 7.30-7.41(m, 5H), 5.82 (d, J = 14.6 Hz, 1H), 5.59 (dd, J = 14.6, 7.0 Hz, 1H), 5.18 (m, 1H), 1.88 (bs, 1H), 1.05 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 149.2, 143.8, 128.6, 127.6, 127.3, 126.4, 75.6, 33.1, 29.6.
IR (NaCl, thin film): 3657, 2954, 2876, 1457, 1238, 966, 737, 691.
HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{32}OSiNa$, 327.2115; found, 327.2105.

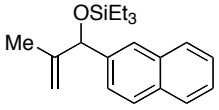


2r'



2r

A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (28 mg, 0.1 mmol, 20 mol%), dicyclohexylphenylphosphine (56 mg, 0.2 mmol, 40 mol%) and 2-naphthaldehyde (78 mg, 0.5 mmol, 100 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (2.5 mL) under argon and stirred 5 min at room temperature. The system was purged with propene for 1 min. The propene atmosphere was maintained by a propene balloon. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. TESOTf (197 μL, 0.875 mmol, 175 mol%) was added. The mixture was stirred at room temperature for 6 h. The mixture was diluted with hexane and filtered through a plug of silica gel. Solvent was removed under reduced pressure. Purification via flash chromatography on silica afforded **2r'** in 73% isolated yield as a colorless oil and **2r** in 14% isolated yield as a colorless oil.



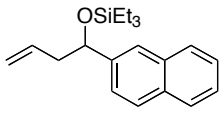
2r'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.86 (m, 4H); 7.50 (m, 3H); 5.33 (s, 1H); 5.26 (s, 1H); 4.94 (s, 1H); 1.62 (s, 3H); 1.00 (t, J = 8.0 Hz, 9H); 0.67 (dq, J = 1.8, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 148.0, 141.0, 133.4, 133.0, 128.2, 127.8, 127.8, 126.0, 125.7, 124.9, 124.8, 78.6, 17.6, 7.1, 5.1.

IR (NaCl, thin film): 2955, 2912, 2876, 1652, 1508, 1457, 1238, 1084, 1005, 899, 742.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{28}OSiNa$, 335.1802; found, 335.1809.



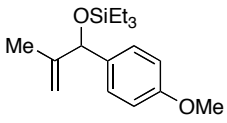
2r

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.83 (t, *J* = 8.5 Hz, 3H); 7.75 (s, 1H); 7.48 (m, 3H); 5.81 (m, 1H); 5.05 (m, 1H); 5.02 (m, 1H); 4.86 (t, *J* = 5.9 Hz); 2.55 (m, 2H); 0.91 (t, *J* = 8.0 Hz, 9H); 0.57 (dq, *J* = 3.5, 7.5 Hz, 6H).

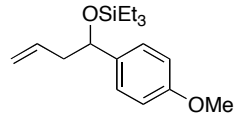
^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.8, 135.3, 133.4, 133.0, 128.1, 127.9, 127.9, 126.1, 125.7, 124.6, 75.2, 45.6, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2876, 1458, 1239, 1084, 1005, 914, 817, 743.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{20}H_{28}OSiNa$, 335.1802; found, 335.1808.

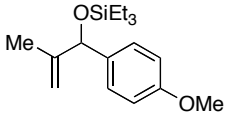


2s'



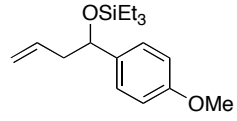
2s

The reaction of propene (1atm, balloon) and *p*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, Cy_2PhP (56 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the procedure for **2r'** above afforded **2s'** and **2s** and the ratio of **2s'**:**2s** is 82:18. Purification via flash chromatography on silica afforded **2s'** and **2s** as a colorless mixture in 95% isolated yield.



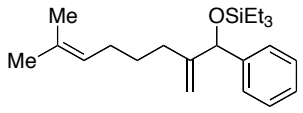
2s'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (d, *J* = 8.7 Hz, 2H); 6.90 (d, *J* = 8.7 Hz, 2H); 5.22 (s, 1H); 5.08 (s, 1H); 4.96 (s, 1H); 3.62 (s, 3H); 2.15 (s, 1H); 1.62 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.3, 147.2, 134.3, 127.9, 113.9, 110.8, 77.5, 55.4, 18.7.

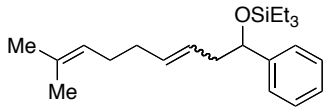


2s

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (d, *J* = 8.7 Hz, 2H); 6.90 (d, *J* = 8.7 Hz, 2H); 5.82 (m, 1H); 5.15 (m, 2H); 4.69 (t, *J* = 6.5 Hz, 1H); 2.52 (d, *J* = 6.8 Hz, 2H), 2.15 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.1, 136.2, 134.8, 127.3, 118.4, 113.9, 73.1, 55.4, 43.9.



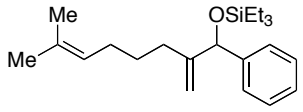
2t'



2t

A 10 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (27.5 mg, 0.2 mmol, 20 mol%) and dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in toluene (1.0 mL) under argon and stirred 5 min at room temperature. 7-methyl-1,7-octadiene (825 μL, 5 mmol, 1000 mol%) was added. Triethylamine (418 μL, 3 mmol, 600 mol%) was added. TESOTf (197 μL, 0.875 mmol, 175 mol%) was added. Benzaldehyde (51 μL, 0.5 mmol, 100 mol%) in 1.5 mL toluene was added to the reaction mixture over 6 min. The mixture was stirred at room temperature for 18 h. The mixture was filtered through a plug of silica gel. Solvent was removed under reduced pressure and ^{1}H NMR of the crude mixture indicated the ratio of **2t'**:**2t** is 71:29. Purification via flash chromatography on silica afforded **2t'** in 50% isolated yield as a colorless oil and **2t** in 22% isolated yield as a colorless oil.

This reaction can be run according to general procedure 3, which also afforded **2t'** and **2t** in similar yield.



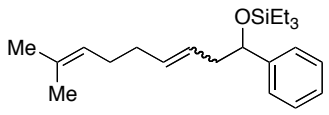
2t'

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40 (d, J = 7.0 Hz, 2H); 7.34 (t, J = 7.8 Hz, 2H); 7.27 (t, J = 7.2, 1H); 5.26 (bs, 1H); 5.18 (bs, 1H); 5.10 (t, J = 7.2 Hz, 1H); 4.81 (bs, 1H); 1.76-2.10 (m, 4H); 1.71 (s, 3H); 1.60 (s, 3H); 1.44 (quintet, J = 7.7 Hz, 2H); 0.97 (t, J = 7.9 Hz, 9H); 0.62 (dq, J = 1.5, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 152.1, 143.7, 131.6, 128.1, 127.1, 126.6, 124.8, 109.5, 78.2, 30.4, 28.2, 28.1, 25.9, 17.8, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2877, 1647, 1456, 1091, 1067, 743.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{36}OSiNa$, 367.2427; found, 367.2431.



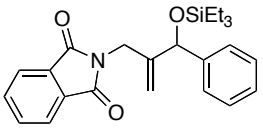
2t

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30 (m, 5H); 5.45 (m, 2H); 5.15 (t, *J* = 7.1 Hz, 1H); 4.64 (dd, *J* = 5.4, 7.3 Hz, 1H); 2.45 (quintet, *J* = 5.4 Hz, 1H); 2.35 (quintet, *J* = 5.9 Hz, 1H); 2.05 (m, 4H); 1.62 (s, 3H); 1.72 (s, 3H); 0.92 (t, *J* = 7.9 Hz, 9H); 0.55 (dq, *J* = 1.5, 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.6, 132.8, 131.7, 128.1, 127.1, 126.9, 126.1, 124.4, 75.6, 44.5, 33.1, 28.2, 25.9, 17.9, 7.0, 5.0.

IR (NaCl, thin film): 2955, 2914, 2876, 1454, 1089, 1005, 969, 699.

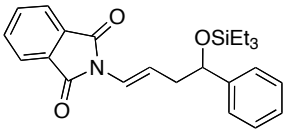
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{22}H_{36}OSiNa$, 367.2427; found, 367.2430.



4a

The reaction of allylphthalimide (281 mg, 1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4a** and **4a'** in 67% total yield according to ^{1}H NMR of the crude mixture and the ratio of **4a**:**4a'** is 74:26. Purification via flash chromatography on silica afforded **4a** as a mixture of **4a** and the isomerized starting material.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.77 (dd, *J* = 3.0, 5.4 Hz, 2H); 7.73 (dd, *J* = 3.0, 5.4 Hz, 2H); 7.13-7.41 (m, 5H); 5.36 (s, 1H), 5.30 (s, 1H), 4.99 (s, 1H), 4.26 (d, *J* = 16 Hz, 1H), 4.08 (d, *J* = 16 Hz, 1H), 0.91 (t, *J* = 7.9 Hz, 9H); 0.59 (q, *J* = 7.9 Hz, 6H).



4a'

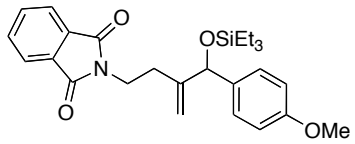
The reaction of allylphthalimide (1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4a** and **4a'** in 43% total yield according to ^{1}H NMR of the crude mixture and the ratio of **4a**:**4a'** is 12:88. The *E* / *Z* ratio of **4a'** is 60:40. Purification via flash chromatography on silica afforded **4a'** as a mixture with the isomerized starting material.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.86 (dd, *J* = 3.1, 5.4 Hz, 2H); 7.73 (dd, *J* = 3.1, 5.4 Hz, 2H); 7.25–7.37 (m, 5H); 6.62 (m, 2H); 4.76 (dd, *J* = 5.5, 6.9 Hz, 1H); 2.47-2.60 (m, 2H); 0.89 (t, *J* = 8.0 Hz, 9H); 0.56 (q, *J* = 2.8, 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.7, 149.2, 145.0, 134.5, 131.9, 128.2, 127.3, 126.1, 123.7, 119.5, 118.8, 75.0, 43.1, 7.0, 5.0.

IR (NaCl, thin film): 2954, 2876, 1781, 1721, 1384, 1088, 1069, 715, 701.

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{14}NO_2Na$, 276.1025; found, 276.1022.



4b

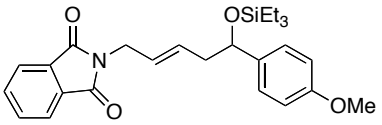
The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4b** and **4b'** in 54% total yield according to ^{1}H NMR of the crude mixture and the ratio of **4b**:**4b'** is 71:29. Purification via flash chromatography on silica afforded **4b** and **4b'.**

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.81 (dd, *J* = 3.0, 5.4, 2H); 7.70 (dd, *J* = 3.0, 5.4, 2H); 7.26 (d, *J* = 8.7 Hz, 2H); 6.79 (d, *J* = 8.7 Hz, 2H); 5.27 (s, 1H); 5.15 (s, 1H); 4.99 (s, 1H); 3.66-3.86 (m, 2H); 3.78 (s, 3H); 2.33-2.40 (m, 1H); 2.16-2.23 (m, 1H); 0.90 (t, *J* = 7.9 Hz, 9H); 0.57 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 168.4, 158.8, 148.6, 135.2, 134.0, 132.3, 127.7, 123.3, 113.5, 111.8, 77.6, 55.3, 37.2, 29.8, 7.0, 5.0.

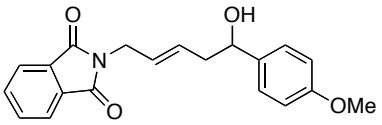
IR (NaCl, thin film): 2954, 2876, 1773, 1715, 1511, 1467, 1431, 1395, 1354, 1247, 1078, 952, 719.

HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{26}H_{33}O_4SiNa$, 474.2066; found, 474.2071.



(4b')

The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4b** and **4b'** in 76% total yield according to ^1H NMR of the crude mixture and the ratio of **4b**:**4b'** is <5:95. Treatment of 4b' with TBAF followed by flash chromatography on silica afforded desilylated **4b'**.

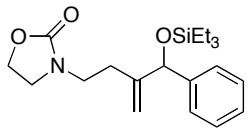


desilylated **4b'**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.86 (dd, *J* = 3.1, 5.4 Hz, 2H); 7.73 (dd, *J* = 3.1, 5.4 Hz, 2H); 7.25 (d, *J* = 8.7 Hz, 2H); 6.84 (d, *J* = 8.7 Hz, 2H); 5.73(dt, *J* = 6.0, 15.4 Hz, 1H); 5.62 (dt, *J* = 6.0, 15.4 Hz, 1H); 4.68 (dd, *J* = 6.4, 6.4 Hz, 1H); 4.25-4.33 (m, 2H); 3.78 (s, 3H); 2.46 (m, 2H), 2.09 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 168.2, 159.1, 136.1, 134.1, 132.3, 130.8, 127.2, 127.1, 123.5, 113.9, 73.1, 55.4, 42.3, 39.7.

IR (NaCl, thin film): 3466, 2929, 1770, 1711, 1611, 1512, 1395, 1249, 1174, 1034, 833, 720.



4c

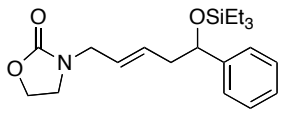
The reaction of homoallyloxazolidinone (1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded **4c** and **4c'** in 60% total yield according to ^{1}H NMR of the crude mixture and the ratio of **4c**:**4c'** is 83:17. Purification via flash chromatography on silica afforded **4c** and **4c'** as colorless oils.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.23-7.38 (m, 5H); 5.31 (s, 1H); 5.20 (s, 1H); 5.00 (s, 1H); 4.16-4.21 (m, 2H); 3.19-3.36 (m, 4H); 2.02-2.26 (m, 2H); 0.93 (t, J = 7.9 Hz, 9H); 0.60 (q, J = 7.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.4, 148.1, 143.1, 128.2, 127.4, 126.3, 112.0, 78.1, 61.8, 44.3, 42.8, 27.9, 7.0, 4.9.

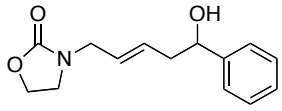
IR (NaCl, thin film): 2955, 2912, 2876, 1753, 1484, 1426, 1265, 1089, 1067, 1044, 1007, 861, 744, 701.

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{31}NO_3Na$, 384.1965; found, 384.1951.



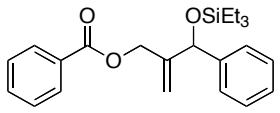
4c'

The reaction of homoallylphthalimide (1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded **4c** and **4c'** in 28% total yield according to ^1H NMR of the crude mixture and the ratio of **4c**:**4c'** is 10:90. 4c' was subjected to TBAF and purification via flash chromatography on silica afforded a desilylated **4c'**.



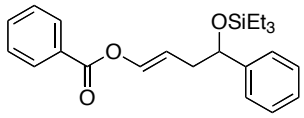
desilylated **4c'**

^1H NMR (400 MHz, $CDCl_3$, δ): 7.28-7.42 (m, 5H), 5.68 (dt, *J* = 5.7, 7.1 Hz, 1H), 5.49 (dt, *J* = 5.7, 7.1 Hz, 1H), 4.77 (dd, *J* = 6.7, 6.8 Hz, 1H), 4.28 (t, *J* = 8.0 Hz, 2H), 3.80-3.82 (m, 2H), 3.38 (dt, *J* = 2.5, 8.0 Hz, 2H), 2.53-2.59 (m, 2H), 2.11-2.17 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.4, 143.9, 131.2, 128.7, 127.8, 127.3, 126.0, 73.8, 61.9, 46.4, 44.2, 42.1.
IR (NaCl, thin film): 3421, 2919, 2361, 1734, 1653, 1490, 1437, 1259, 1038, 762, 702.
HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{17}NO_3Na$, 270.1101; found, 270.1104.



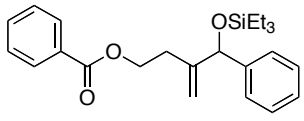
4d

The reaction of allylbenzoate (2.5 mmol, 500 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene following the general procedure 3 above afforded **4d** and **4d'** in <5% total yield according to ^{1}H NMR of the crude mixture. **4d** and **4d'** were not isolated from the reaction mixture.



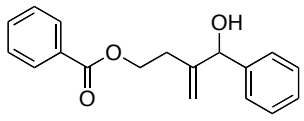
4d'

The reaction of allylbenzoate (2.5 mmol, 500 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4d** and **4d'** in <5% total yield according to ^{1}H NMR of the crude mixture. **4d** and **4d'** were not isolated from the reaction mixture.



4e

The reaction of homoallylbenzoate (1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, dicyclohexylphenylphosphine (55 mg, 0.4 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at room temperature following the general procedure 3 above afforded **4e** and **4e'** in 21% total yield according to ^{1}H NMR of the crude mixture. **4e** was subjected to TBAF and the free alcohol was isolated as a colorless oil.



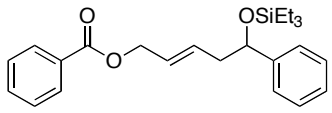
desilylated **4e**

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.02 (d, *J* = 7.3 Hz, 2H); 7.58 (t, *J* = 7.3 Hz, 1H); 7.28 (m, 7H); 5.37 (s, 1H); 5.29 (s, 1H); 5.12 (s, 1H); 4.36-4.50 (m, 2H); 2.34-2.51 (m, 2H); 2.29 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.9, 147.0, 141.8, 133.1, 130.4, 129.7, 128.7, 128.5, 128.0, 126.7, 113.3, 77.6, 63.7, 31.3.

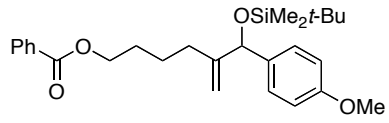
IR (NaCl, thin film): 3447, 3063, 3030, 2961, 1717, 1701, 1451, 1316, 1276, 1117, 1071, 1026, 912, 712, 701, 668.

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{18}O_3Na$, 305.1148; found, 305.1156.



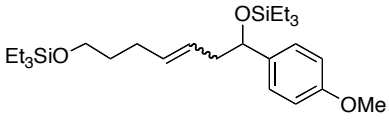
4e'

The reaction of homoallylbenzoate (1.5 mmol, 300 mol%) and benzaldehyde (51 μL, 0.5 mmol) with $Ni(cod)_2$, Ph_3P (52 mg, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4e** and **4e'** in <5% total yield according to ^{1}H NMR of the crude mixture and. **4e'** was not isolated from the reaction mixture.

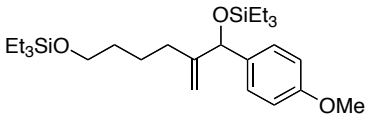


4f

The reaction of 1-hexen-6-benzoate (510.3 mg, 2.5 mmol, 500 mol%) and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol, 175 mol%), triethylamine in toluene following the general procedure 3 above afforded **4f** and **4f'** in 44% total isolated yield after flash chromatography on silica and according to ^{1}H NMR of the crude mixture the ratio of **4f**:**4f'** is 73:27. **4f** and **4f'** were isolated together as a mixture.

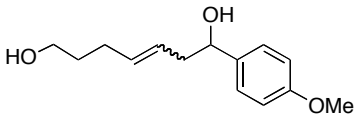


4g



4g'

The reaction of triethyl-hex-5-enyloxy-silane (1.5 mmol, 300 mol%) and *o*-anisaldehyde (61 μL, 0.5 mmol) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol, 175 mol%), triethylamine in toluene at 35 °C following the general procedure 3 above afforded **4g** and **4g'** in 66% total yield according to ^{1}H NMR of the crude mixture and the ratio of **4g**:**4g'** is 92:8. The *E* / *Z* ratio of **4g** is 50:50. **4g'** was not isolated from the mixture. **4g** were subjected to TBAF and the free diols was isolated via flash chromatography on silica as a colorless oil.



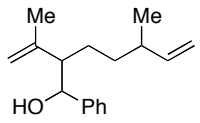
desilylated **4g**

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.26-7.28 (m, 2H); 6.89 (d, *J* = 8.6 Hz, 2H); 5.41-5.63 (m, 2H), 4.70 (dd, *J* = 4.8, 8.0 Hz, 0.5 H), 4.64 (dd, *J* = 7.2, 7.2 Hz, 0.5 H), 3.81 (s, 3H), 3.60-3.65 (m, 2H), 2.39-2.62 (m, 2H), 2.10-2.27 (m, 2H), 1.89 (bs, 2H), 1.58-1.67 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.2, 159.2, 136.5, 136.4, 134.2, 132.5, 127.2, 127.2, 126.6, 126.1, 114.0, 113.9, 73.7, 73.4, 62.7, 62.0, 55.5, 42.8, 37.3, 32.3, 32.1, 29.5, 23.7.

IR (NaCl, thin film): 3354, 2933, 1612, 1513, 1442, 1303, 1247, 1175, 1035, 832.

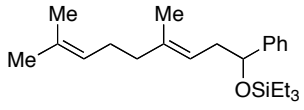
HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{48}O_3Si_2Na$, 487.3040; found, 487.3017.



5a

To β-Citronellene (0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Me_2AlCl (1.0 M in hexane, 1.1 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. The reaction was quenched by diluting the reaction mixture with diethylether, followed by slow addition of water until gas evolution ceased. The organic layer was separated, and the aqueous layer was extracted with ether twice. The combined organic layers were washed with brine, dried and evaporated in vacuo. Purification via flash chromatography on silica gel afforded the coupling product **5a** as a colorless oil. Homoallylic alcohol **5b** was not detected.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.28-7.39 (m, 5H); 5.45-5.61 (m, 1H); 5.09 (s, 1H); 5.00 (s, 1H); 4.79-4.94 (m, 2H); 4.38 (dd, J = 0.7, 8.5 Hz, 1H); 2.19-2.35 (m, 1H); 1.89-2.05 (m, 1H); 1.73, 1.75 (two s, 3H); 1.67 (bs, 1H); 0.91-1.27 (m, 4H); 0.87, 0.84 (two d, J = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.1, 144.3, 142.9, 128.5, 127.9, 127.4, 127.3, 126.0, 116.5, 116.4, 113.1, 112.4, 75.5, 75.4, 56.5, 56.4, 37.8, 37.5, 34.2, 34.2, 31.2, 26.3, 21.0, 19.5, 18.3, 18.1.
HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{24}ONa$, 244.1822; found, 244.1817.



5b

The reaction of β-Citronellene and benzaldehyde (51 μL, 0.5 mmol, 100 mol%) with $Ni(cod)_2$, $EtOPh_2P$ (43 μl, 0.2 mmol, 40 mol%) and TESOTf (197 μL, 0.875 mmol, 175 mol%), triethylamine in toluene following the general procedure 3 above afforded **5b** 75% total yield according to ^{1}H NMR of the crude mixture and the E/Z ratio of **5b** is 71:29. **5a** was not detected. Purification via flash chromatography on silica afforded **5b** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.25-7.36 (m, 5H); 5.18-5.20 (m, 1H); 5.12-5.12 (m, 1H); 4.64-4.68 (m, 1H); 2.37-2.48 (m, 2H); 2.01-2.10 (m, 4H); 1.73 (m, 4H); 1.64 (m, 3H); 1.55 (s, 2H); 0.92 (t, J = 6.9 Hz, 9H); 0.57 (dq, J = 3.0, 6.9 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 145.8, 145.8, 137.2, 137.1, 131.7, 131.5, 128.1, 128.0, 127.0, 127.0, 126.1, 126.1, 124.6, 124.5, 121.8, 120.7, 75.5, 75.3, 40.0, 39.8, 39.7, 32.3, 26.8, 26.7, 25.9, 25.9, 23.6, 17.8, 17.8, 16.3, 7.0, 7.0, 5.0, 5.0.
IR (NaCl, thin film): 2955, 2876, 1454, 1376, 1239, 1088, 1068, 1006, 829, 743, 700.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{28}OSiNa$, 381.2590; found, 381.2583.

SN050690

1a


```
Current Data Parameters
NAME              SN690-H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20050707
Time                19.56
INSTRUM             spect
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PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     4
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                  45.3
DW                60.400 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec

============ CHANNEL f1 =============
NUC1                1H
P1                9.50 usec
PL1               2.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P              10.000 ppm
F1              4001.30 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM         200.06500 Hz/cm
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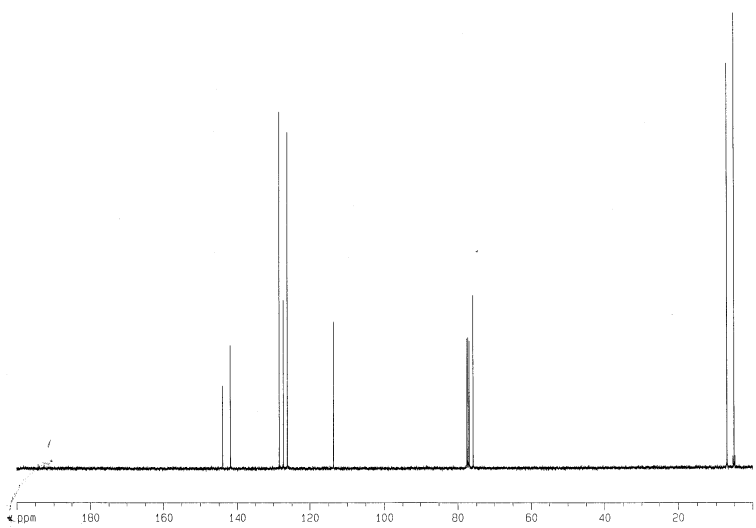
SN050690

1a

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Current Data Parameters
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EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   874
DS                     4
SWH          24330.900 Hz
FIDRES        0.371260 Hz
AQ            1.3468148 sec
RG                  1024
DW                20.550 usec
DE                 6.00 usec
TE                300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

============ CHANNEL f1 =============
NUC1                13C
P1                8.50 usec
PL1               3.00 dB
SFO1        100.6237959 MHz

============ CHANNEL f2 =============
CPDPRG2         waltz16
NUC2                1H
PCPD2          100.00 usec
PL2               2.00 dB
PL12             22.00 dB
PL13             22.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF          100.6127533 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
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F2                0.00 Hz
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HZCM         1006.12756 Hz/cm
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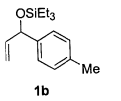
SN050714



1b


```
Current Data Parameters
NAME              SN714-H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20050716
Time                21.05
INSTRUM             spect
PROBHD     5mm BBO BB-1
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  35.9
DW                60.400 usec
DE                 6.00 usec
TE                300.0 K
D1             1.00000000 sec

============ CHANNEL f1 ========
NUC1                   1H
P1                  7.90 usec
PL1                 0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300051 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P               10.000 ppm
F1                4001.30 Hz
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F2                 0.00 Hz
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HZCM          200.06500 Hz/cm
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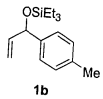
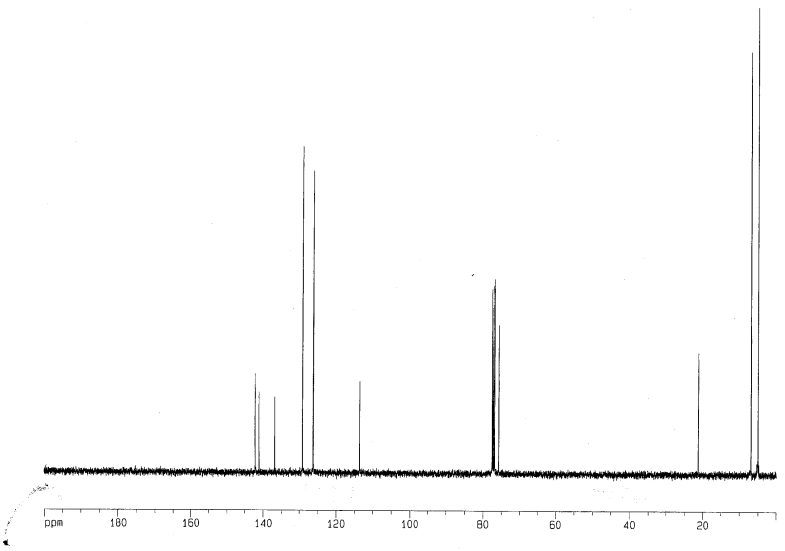
SN050714



1b

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Current Data Parameters
NAME              SN714-C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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Time                20.58
INSTRUM             spect
PROBHD     5mm BBO BB-1
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   109
DS                     4
SWH            25125.629 Hz
FIDRES          0.383387 Hz
AQ              1.3042164 sec
RG                  2048
DW                19.900 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

============ CHANNEL f1 ============
NUC1                  13C
P1                 15.25 usec
PL1                 3.00 dB
SFO1         100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2           waltz16
NUC2                   1H
PCPD2              107.50 usec
PL2                 0.00 dB

PL13               24.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127492 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
F1P               200.000 ppm
F1              20122.55 Hz
F2P                0.000 ppm
F2                 0.00 Hz
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HZCM          1006.12744 Hz/cm
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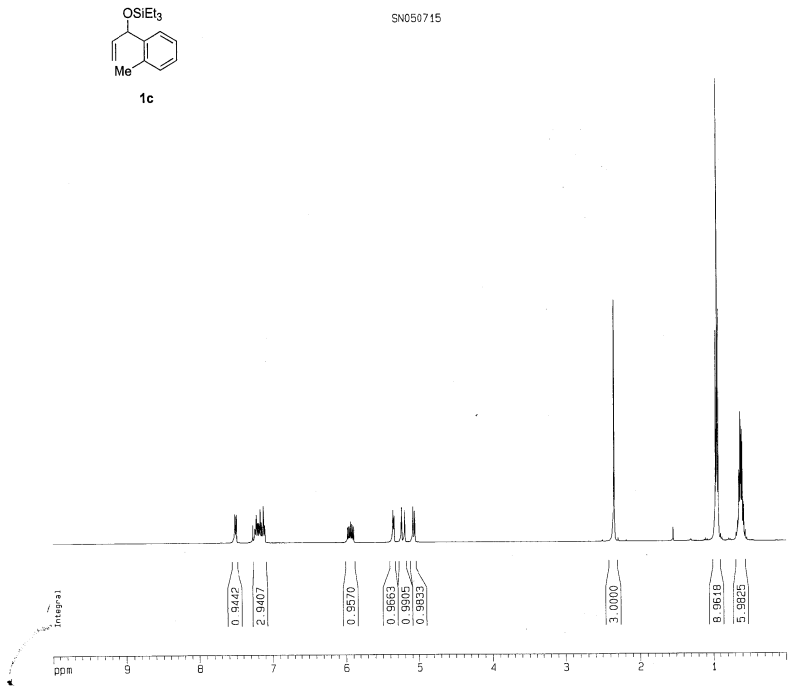


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Current Data Parameters
NAME                 SN715-H
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20050716
Time                 21.18
INSTRUM              spect
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PULPROG              zg30
TD                   65536
SOLVENT              CDCl3
NS                         8
DS                         2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      50.6
DW                   60.400 usec
DE                    6.00 usec
TE                   300.0 K
D1                1.00000000 sec

============ CHANNEL f1 ========
NUC1                      1H
P1                     7.90 usec
PL1                    0.00 dB
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300054 MHz
WDW                        EM
SSB                         0
LB                      0.30 Hz
GB                          0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                   10.000 ppm
F1                  4001.30 Hz
F2P                   0.000 ppm
F2                    0.00 Hz
PPMCM              0.50000 ppm/cm
HZCM             200.06500 Hz/cm
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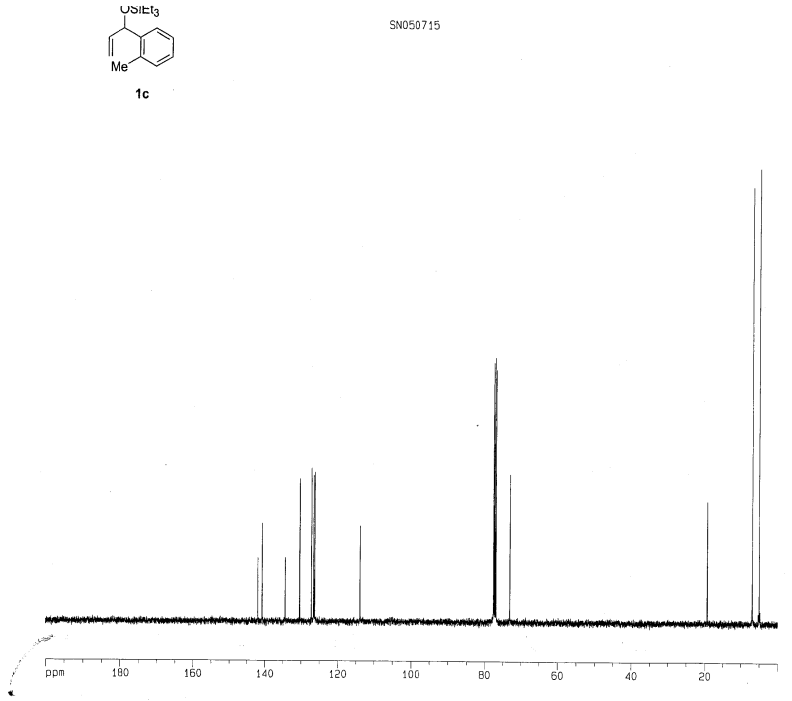


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Current Data Parameters
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EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
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Time                 21.28
INSTRUM              spect
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PULPROG          zgpg30
TD                   65536
SOLVENT              CDCl3
NS                       297
DS                         4
SWH              25125.629 Hz
FIDRES            0.383387 Hz
AQ                1.3042164 sec
RG                    1290.2
DW                   19.900 usec
DE                    6.00 usec
TE                   300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

============ CHANNEL f1 ============
NUC1                      13C
P1                    15.25 usec
PL1                    3.00 dB
SFO1            100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2               waltz16
NUC2                      1H
PCPD2                107.50 usec
PL2                    0.00 dB
PL12                  24.00 dB
PL13                  24.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                100.6127476 MHz
WDW                        EM
SSB                         0
LB                      1.00 Hz
GB                          0
PC                      1.40

1D NMR plot parameters
CX                     20.00 cm
F1P                   200.000 ppm
F1                  20122.55 Hz
F2P                   0.000 ppm
F2                    0.00 Hz
PPMCM             10.00000 ppm/cm
HZCM             1006.12744 Hz/cm
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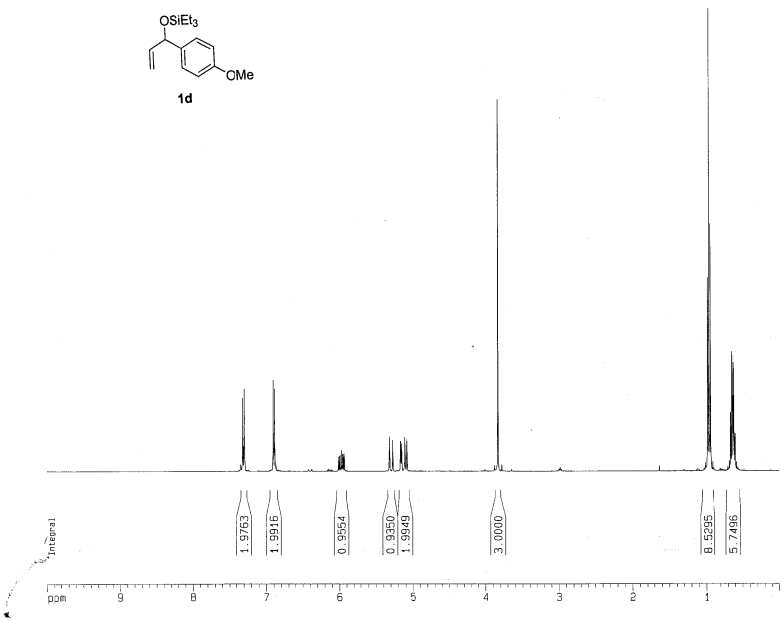
SN050729

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Current Data Parameters
NAME                  SN729-H
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_               20050724
Time                   19.06
INSTRUM                spect
PROBHD     5mm BBO BB-1
PULPROG                zg30
TD                     65536
SOLVENT                CDCl3
NS                         8
DS                         2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                      40.3
DW                    60.400 usec
DE                     6.00 usec
TE                    300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 ========
NUC1                       1H
P1                       7.90 usec
PL1                      0.00 dB
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                 400.1300000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00

1D NMR plot parameters
CX                         20.00 cm
F1P                        10.000 ppm
F1                       4001.30 Hz
F2P                         0.000 ppm
F2                          0.00 Hz
PPMCM                0.50000 ppm/cm
HZCM               200.06500 Hz/cm
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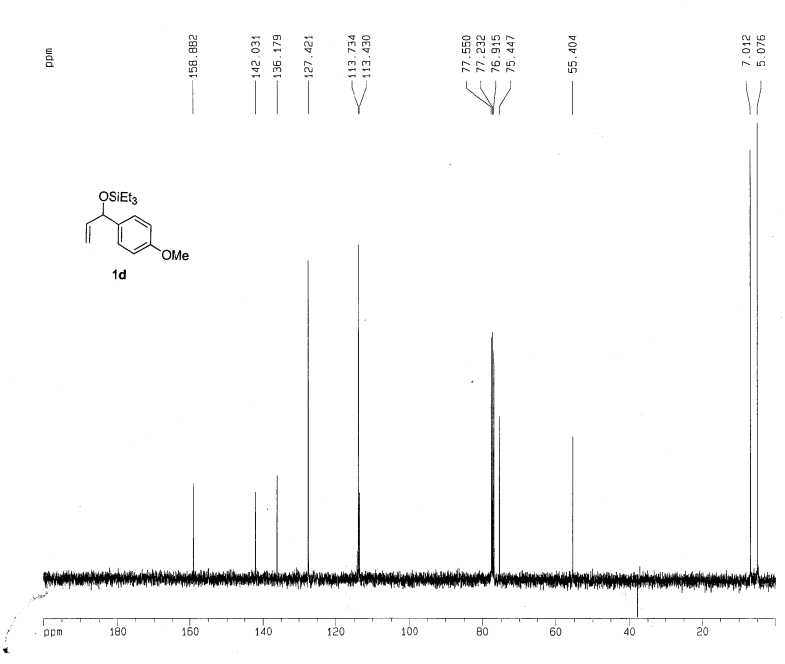
SN050729

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Current Data Parameters
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EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
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Time                   19.26
INSTRUM                spect
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PULPROG              zgpg30
TD                     65536
SOLVENT                CDCl3
NS                        28
DS                         4
SWH               25125.629 Hz
FIDRES             0.383387 Hz
AQ                 1.3042164 sec
RG                      2048
DW                    19.900 usec
DE                     6.00 usec
TE                    300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
d12                0.00002000 sec

============ CHANNEL f1 ============
NUC1                       13C
P1                       15.25 usec
PL1                       3.00 dB
SFO1             100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  107.50 usec
PL2                      0.00 dB
PL12                    24.00 dB
PL13                    24.00 dB
SFO2             400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                 100.6127515 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40

1D NMR plot parameters
CX                         20.00 cm
F1P                       200.000 ppm
F1                      20122.55 Hz
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F2                          0.00 Hz
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HZCM              1006.12756 Hz/cm
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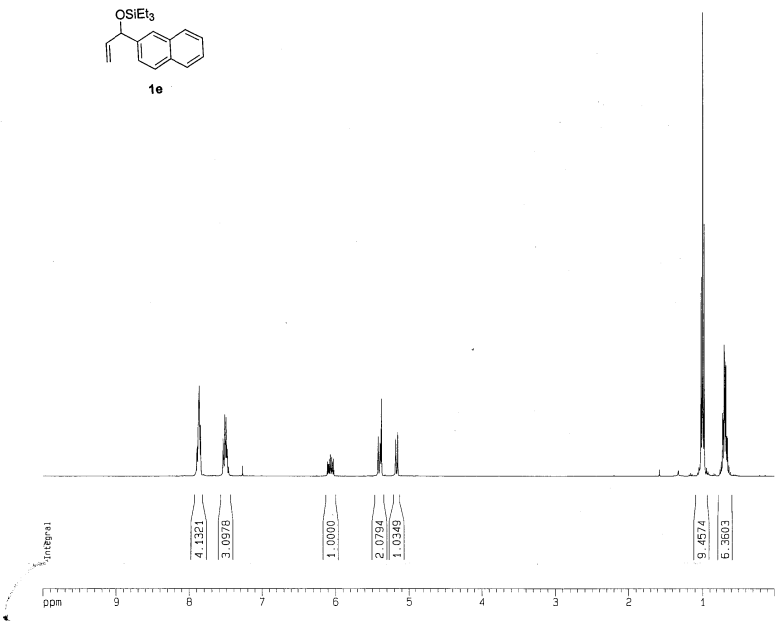
SN050723

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Current Data Parameters
NAME                  SN723-H
EXPNO                       1
PROCNO                      1

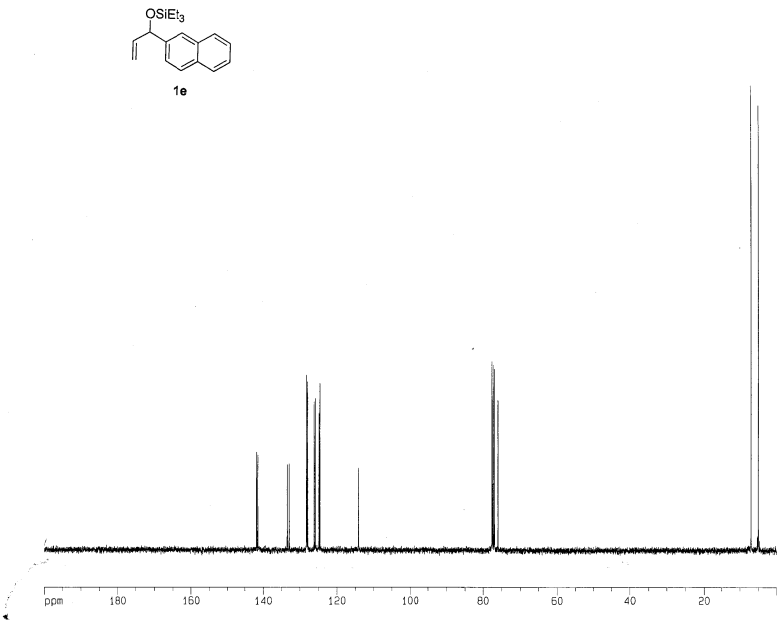
F2 - Acquisition Parameters
Date_              20050721
Time                    22.05
INSTRUM                 spect
PROBHD       5mm BBO BB-1
PULPROG                 zg30
TD                     65536
SOLVENT                 CDCl3
NS                          8
DS                          2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       40.3
DW                     60.400 usec
DE                      6.00 usec
TE                     300.0 K
D1                1.00000000 sec

========== CHANNEL f1 =========
NUC1                       1H
P1                       7.90 usec
PL1                      0.00 dB
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                         32768
SF                400.1300056 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00

1D NMR plot parameters
CX                         20.00 cm
F1P                       10.000 ppm
F1                      4001.30 Hz
F2P                        0.000 ppm
F2                         0.00 Hz
PPMCM                   0.50000 ppm/cm
HZCM                  200.06500 Hz/cm
```

SN050723

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Current Data Parameters
NAME                  SN723-C
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20050721
Time                    22.21
INSTRUM                 spect
PROBHD       5mm BBO BB-1
PULPROG                 zgpg30
TD                     65536
SOLVENT                 CDCl3
NS                        137
DS                          4
SWH               25125.629 Hz
FIDRES            0.383387 Hz
AQ                1.3042184 sec
RG                       4096
DW                     19.900 usec
DE                      6.00 usec
TE                     300.0 K
D1                2.00000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

========== CHANNEL f1 ==========
NUC1                       13C
P1                       15.25 usec
PL1                       3.00 dB
SFO1             100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  107.50 usec
PL2                      0.00 dB
PL12                    24.00 dB
PL13                    24.00 dB
SFO2             400.1316005 MHz

F2 - Processing parameters
SI                         32768
SF                100.6127538 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40

1D NMR plot parameters
CX                         20.00 cm
F1P                      200.000 ppm
F1                     20122.55 Hz
F2P                        0.000 ppm
F2                         0.00 Hz
PPMCM                  10.00000 ppm/cm
HZCM                1006.12756 Hz/cm
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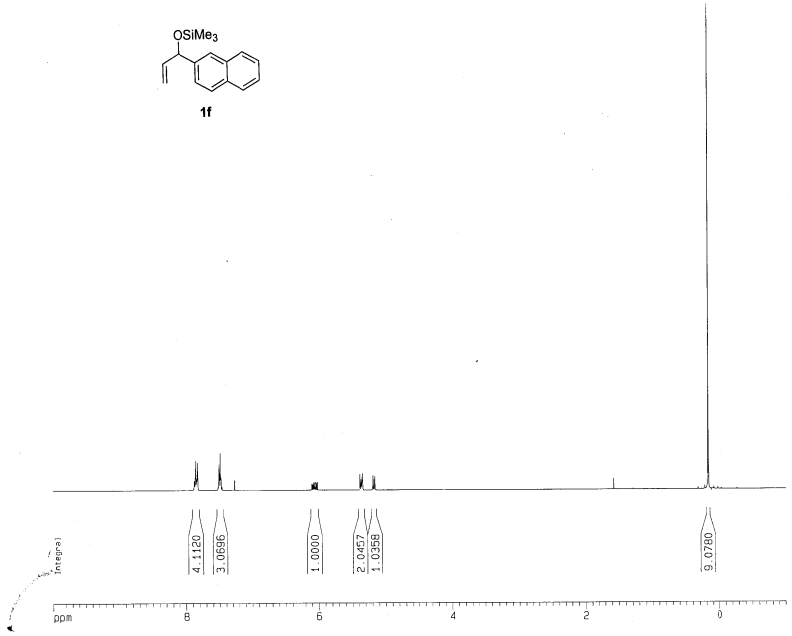
SN050740

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Current Data Parameters
NAME                  SN740-H
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20050729
Time                  22.03
INSTRUM               spect
PROBHD      5mm BBO BB-1
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                          4
DS                          2
SWH              8278.146 Hz
FIDRES           0.126314 Hz
AQ               3.9584243 sec
RG                     71.8
DW                   60.400 usec
DE                    6.00 usec
TE                  300.0 K
D1               1.00000000 sec

============ CHANNEL f1 ========
NUC1                      1H
P1                     7.90 usec
PL1                    0.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF               400.1300059 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                   10.000 ppm
F1                   4001.30 Hz
F2P                   -1.000 ppm
F2                    -400.13 Hz
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HZCM               220.07150 Hz/cm
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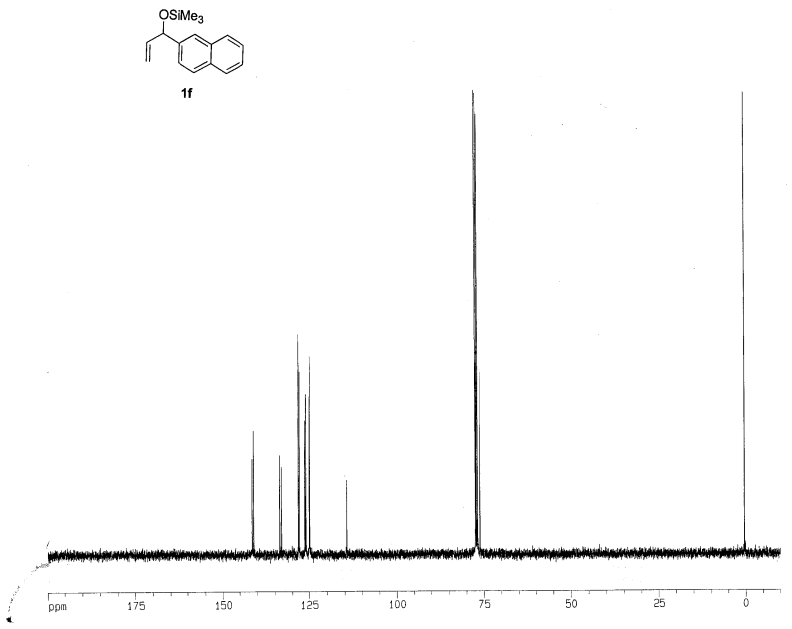
SN050740

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Current Data Parameters
NAME                  SN740-C
EXPNO                       1
PROCNO                      1

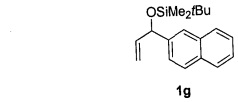
F2 - Acquisition Parameters
Date_              20050729
Time                  22.05
INSTRUM               spect
PROBHD      5mm BBO BB-1
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                         201
DS                          4
SWH             25125.629 Hz
FIDRES           0.383387 Hz
AQ               1.3042164 sec
RG                     16384
DW                   19.900 usec
DE                    6.00 usec
TE                  300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
d12              0.00002000 sec

============ CHANNEL f1 ============
NUC1                      13C
P1                    15.25 usec
PL1                    3.00 dB
SFO1           100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 107.50 usec
PL2                    0.00 dB
PL12                  24.00 dB
PL13                  24.00 dB
SFO2           400.1316005 MHz

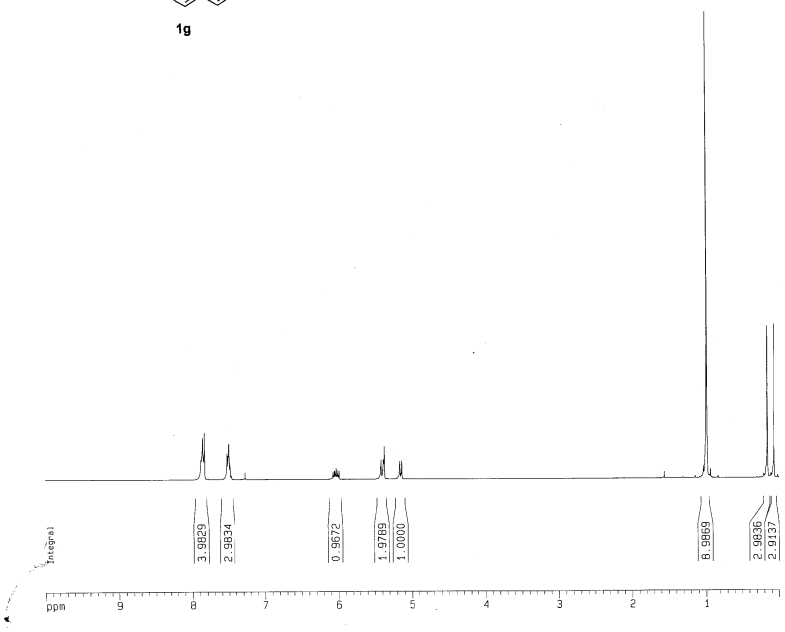
F2 - Processing parameters
SI                        32768
SF               100.6127522 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40

1D NMR plot parameters
CX                     20.00 cm
F1P                   200.000 ppm
F1                   20122.55 Hz
F2P                  -19.000 ppm
F2                   -1906.13 Hz
PPMCM                 10.50000 ppm/cm
HZCM               1056.43396 Hz/cm
```



1g

SN050737



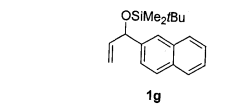

```
Current Data Parameters
NAME              SN737-H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20050727
Time               22.18
INSTRUM            spect
PROBHD     5mm BBO BB-1
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    4
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 50.8
DW                60.400 usec
DE                 6.00 usec
TE                300.0 K
D1            1.00000000 sec

============ CHANNEL f1 ========
NUC1                1H
P1                7.90 usec
PL1                0.00 dB
SFO1        400.1324710 MHz

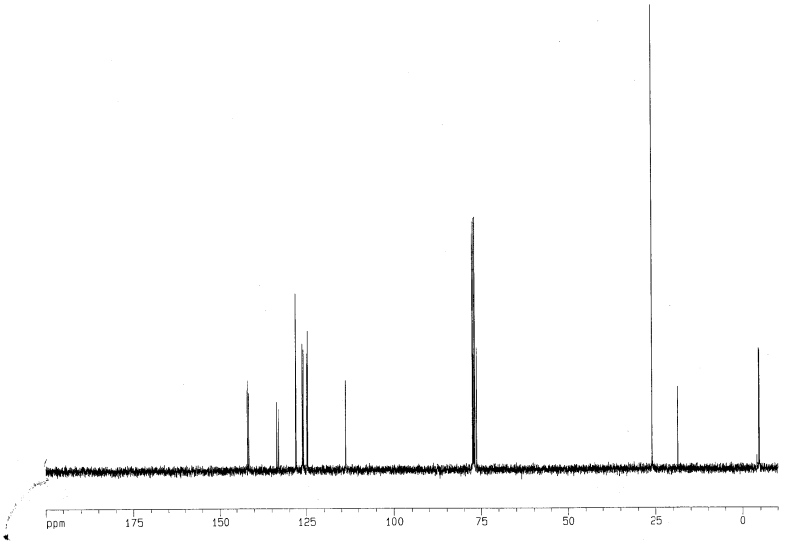
F2 - Processing parameters
SI                32768
SF          400.1300054 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               10.000 ppm
F1              4001.30 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM          200.06500 Hz/cm
```



1g

SN050737




```
Current Data Parameters
NAME              SN737-C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20050727
Time               22.25
INSTRUM            spect
PROBHD     5mm BBO BB-1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  151
DS                    4
SWH          25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG                 3251
DW                19.900 usec
DE                 6.00 usec
TE                300.0 K
D1            2.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec

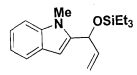
============ CHANNEL f1 ============
NUC1                13C
P1                15.25 usec
PL1                3.00 dB
SFO1        100.6237959 MHz

------------ CHANNEL f2 ------------
CPDPRG2           waltz16
NUC2                1H
PCPD2             107.50 usec
PL2                0.00 dB
PL12              24.00 dB
PL13              24.00 dB
SFO2        400.1316005 MHz

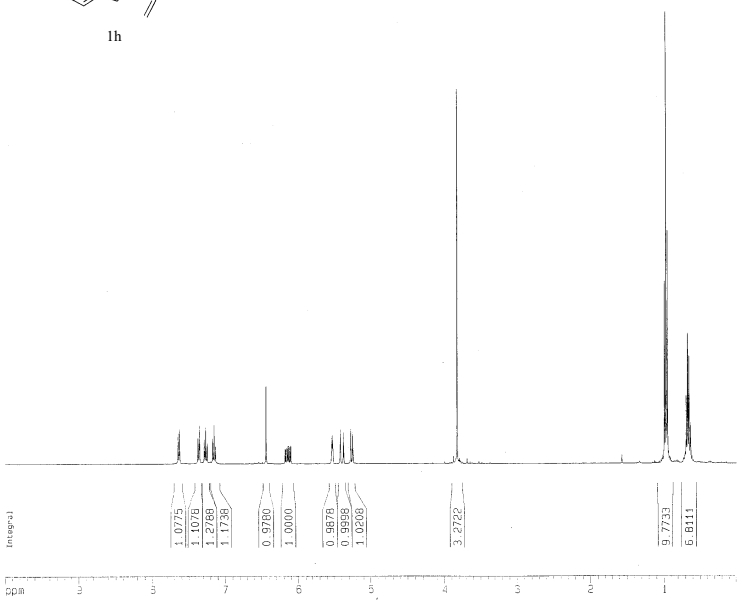
F2 - Processing parameters
SI                32768
SF          100.6127530 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P              -10.000 ppm
F2             -1006.13 Hz
PPMCM          10.50000 ppm/cm
HZCM          1056.43395 Hz/cm
```

SN061116 mixture



1h




```
Current Data Parameters
NAME                 SN1116-H3
EXPNO                        1
PROCNO                       1

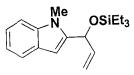
F2 - Acquisition Parameters
Date_               20060331
Time                   20.18
INSTRUM                spect
PROBHD     5mm BBO BB-1
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        4
DS                        2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                 3.9584243 sec
RG                      128
DW                   60.400 usec
DE                    6.00 usec
TE                   300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 ========
NUC1                      1H
P1                     7.90 usec
PL1                    0.00 dB
SFO1            400.1324710 MHz

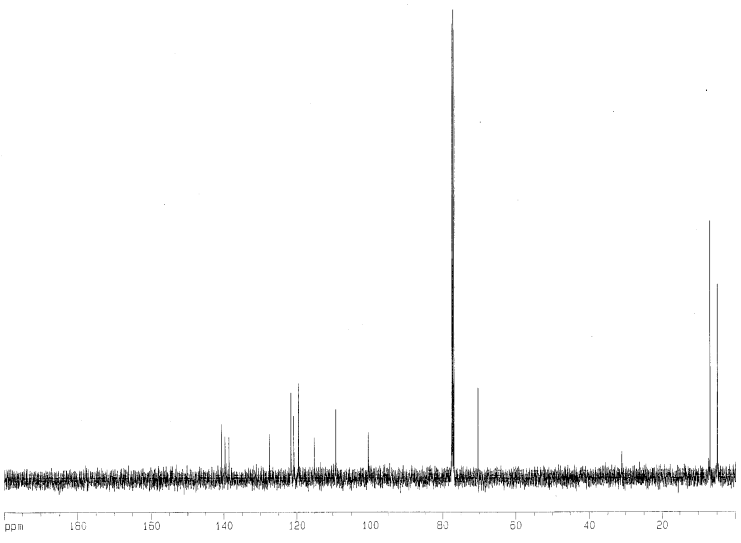
F2 - Processing parameters
SI                        32768
SF                400.1300000 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00

1D NMR plot parameters
CX                      20.00 cm
F1P                    10.000 ppm
F1                   4001.30 Hz
F2P                     0.000 ppm
F2                      0.00 Hz
PPMCM                0.50000 ppm/cm
HZCM               200.06500 Hz/cm
```

SN061116 crude



1h




```
Current Data Parameters
NAME                 SN1116-C
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20060331
Time                   19.32
INSTRUM                spect
PROBHD     5mm BBO BB-1
PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      512
DS                        4
SWH               25125.628 Hz
FIDRES            0.383387 Hz
AQ                 1.3042164 sec
RG                     2048
DW                   19.900 usec
DE                    6.00 usec
TE                   300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
d12                0.00002000 sec

============ CHANNEL f1 ============
NUC1                      13C
P1                    15.25 usec
PL1                    3.00 dB
SFO1            100.6237559 MHz

============ CHANNEL f2 ============
CPDPRG2                waltz16
NUC2                      1H
PCPD2                107.50 usec
PL2                    0.00 dB
PL12                  24.00 dB
PL13                  24.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF                100.6127492 MHz
WDW                        EM
SSB                         0
LB                       1.00 Hz
GB                          0
PC                       1.40

1D NMR plot parameters
CX                      20.00 cm
F1P                   230.000 ppm
F1                  23122.55 Hz
F2P                     0.000 ppm
F2                      0.00 Hz
PPMCM                10.00000 ppm/cm
HZCM               1006.12744 Hz/cm
```

SN050721

1i


```
Current Data Parameters
NAME          SN721-maj-H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20050720
Time                12.24
INSTRUM             spect
PROBHD     5mm BBO BB-1
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                      4
DS                      2
SWH             6278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                   50.8
DW                60.400 usec
DE                 6.00 usec
TE                300.0 K
D1              1.00000000 sec

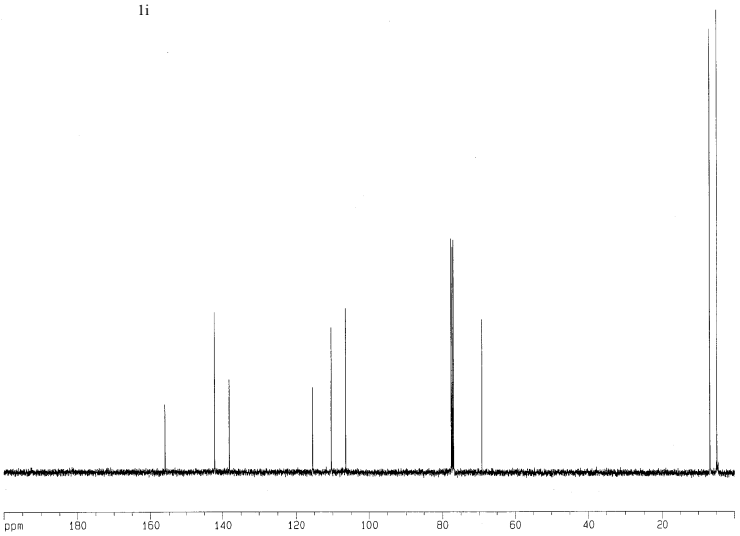
============ CHANNEL f1 ========
NUC1                   1H
P1                   7.90 usec
PL1                  0.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                     32768
SF            400.1300056 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                10.000 ppm
F1                 4001.30 Hz
F2P                 0.000 ppm
F2                  0.00 Hz
PPMCM           0.50000 ppm/cm
HZCM           200.06500 Hz/cm
```

SN050721 major

1i




```
Current Data Parameters
NAME                 SN721-C
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_               20050720
Time                   12.31
INSTRUM                spect
PROBHD     5mm BBO BB-1
PULPROG             zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       140
DS                         4
SWH              25125.629 Hz
FIDRES           0.383387 Hz
AQ               1.3042164 sec
RG                    2048
DW                  19.900 usec
DE                   6.00 usec
TE                  300.0 K
D1               2.00000000 sec
d11              0.03000000 sec
d12              0.00002000 sec

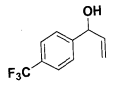
============ CHANNEL f1 ============
NUC1                   13C
P1                   15.25 usec
PL1                   3.00 dB
SFO1          100.6237999 MHz

============ CHANNEL f2 ============
CPDPRG2             waltz16
NUC2                   1H
PCPD2                107.50 usec
PL2                   0.00 dB
PL12                 24.00 dB
PL13                 24.00 dB
SFO2          400.1316005 MHz

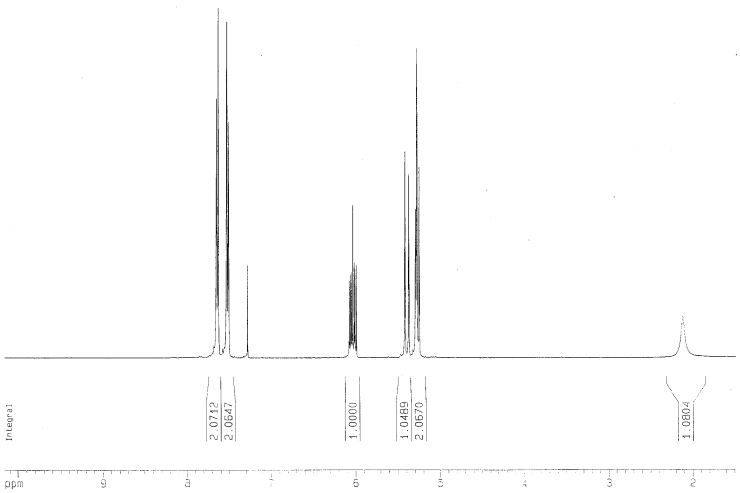
F2 - Processing parameters
SI                     32768
SF            100.6127499 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                200.000 ppm
F1               20122.55 Hz
F2P                 0.000 ppm
F2                  0.00 Hz
PPMCM           10.00000 ppm/cm
HZCM          1006.12744 Hz/cm
```

SN06111B OH



Desilylated 1j




```
Current Data Parameters
NAME          SN1118-OH-H
EXPNO                   1
PROCNO                  1

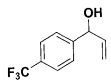
F2 - Acquisition Parameters
Date_          20060403
Time              20.32
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   4
DS                   2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                203.2
DW               60.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec

========== CHANNEL f1 ==========
NUC1                 1H
P1                7.90 usec
PL1               0.00 dB
SFO1        400.1324710 MHz

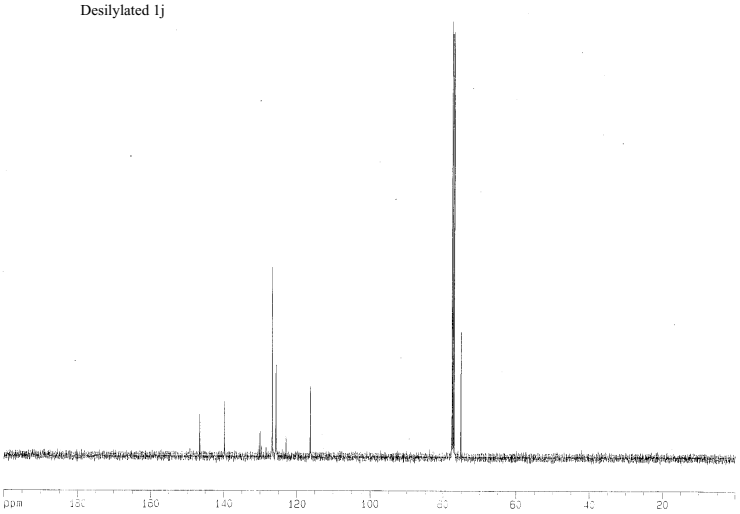
F2 - Processing parameters
SI                32768
SF          400.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX               20.00 cm
F1P             10.165 ppm
F1              4067.20 Hz
F2P              1.490 ppm
F2               596.32 Hz
PPMCM          0.43372 ppm/cm
HZCM         173.54408 Hz/cm
```

SN06111B OH



Desilylated 1j




```
Current Data Parameters
NAME          SN1118-OH-C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20060403
Time              20.22
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 946
DS                   4
SWH          25125.628 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG               1625.5
DW               19.900 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

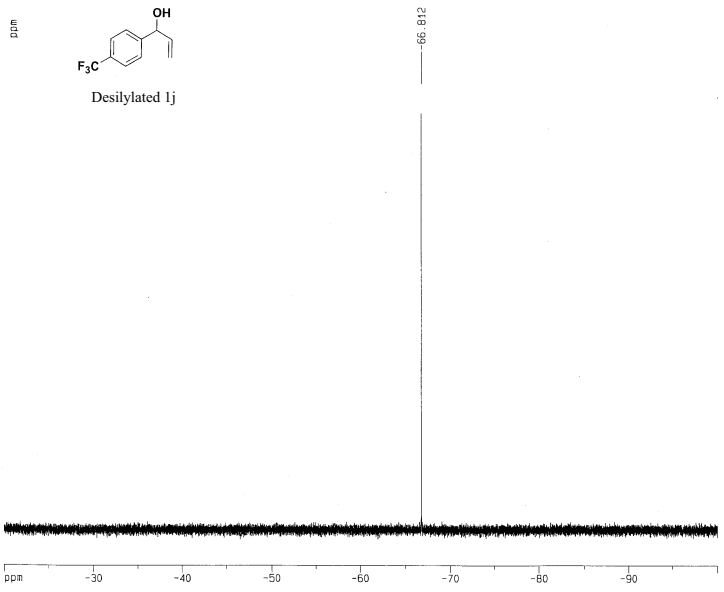
========== CHANNEL f1 ==========
NUC1                13C
P1               15.25 usec
PL1               3.00 dB
SFO1        100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2          waltz16
NUC2                 1H
PCPD2           107.50 usec
PL2               0.00 dB
PL12             24.00 dB
PL13             24.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127982 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX               20.00 cm
F1P             200.000 ppm
F1             20122.55 Hz
F2P              0.000 ppm
F2               0.00 Hz
PPMCM         12.00000 ppm/cm
HZCM        1006.12744 Hz/cm
```

SN061118 OH



Desilylated 1j

```
Current Data Parameters
NAME                SN111B-OH-F
EXPNO                         1
PROCNO                        1

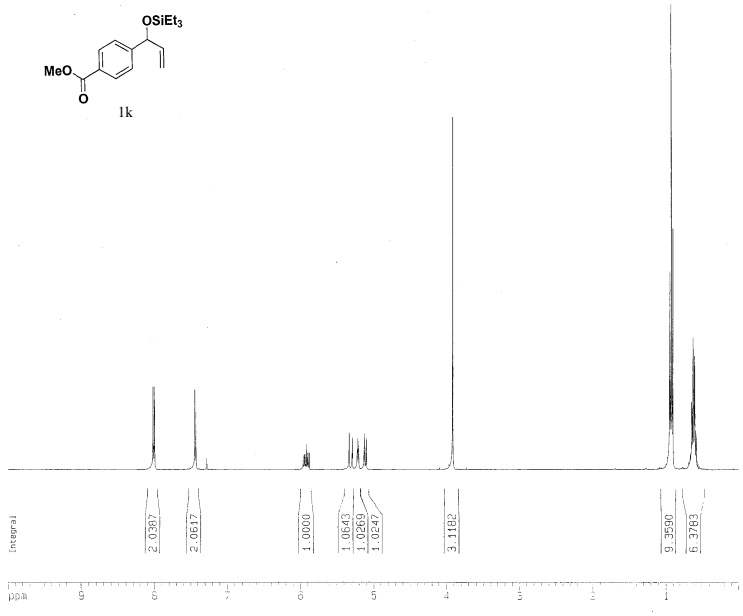
F2 - Acquisition Parameters
Date_              20060403
Time                      18.34
INSTRUM                   spect
PROBHD    5 mm QNP  1H/1
PULPROG                 zgflqn
TD                      131072
SOLVENT                   CDCl3
NS                            28
DS                             4
SWH                75187.969 Hz
FIDRES              0.573639 Hz
AQ                  0.8716788 sec
RG                         6502
DW                     6.650 usec
DE                     6.00 usec
TE                     291.5 K
D1                 1.00000000 sec

======== CHANNEL f1 ========
NUC1                       19F
P1                     19.50 usec
PL1                    -4.00 dB
SFO1              376.4607044 MHz

F2 - Processing parameters
SI                         65536
SF                376.5000000 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00

1D NMR plot parameters
CX                         20.00 cm
CY                         12.50 cm
F1P                      -20.000 ppm
F1                     -7530.00 Hz
F2P                      -100.000 ppm
F2                     -37650.00 Hz
PPMCM                   4.00000 ppm/cm
HZCM                 1506.00000 Hz/cm
```

SN061117



1k

```
Current Data Parameters
NAME              SN1117-H2
EXPNO                     1
PROCNO                    1

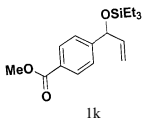
F2 - Acquisition Parameters
Date_              20060403
Time                      18.10
INSTRUM                   spect
PROBHD     5mm BBO BB-1
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                           8
DS                           2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                        57
DW                     60.400 usec
DE                      6.00 usec
TE                     300.0 K
D1                 1.00000000 sec

========== CHANNEL f1 ========
NUC1                       1H
P1                      7.90 usec
PL1                     0.00 dB
SFO1              400.1324710 MHz

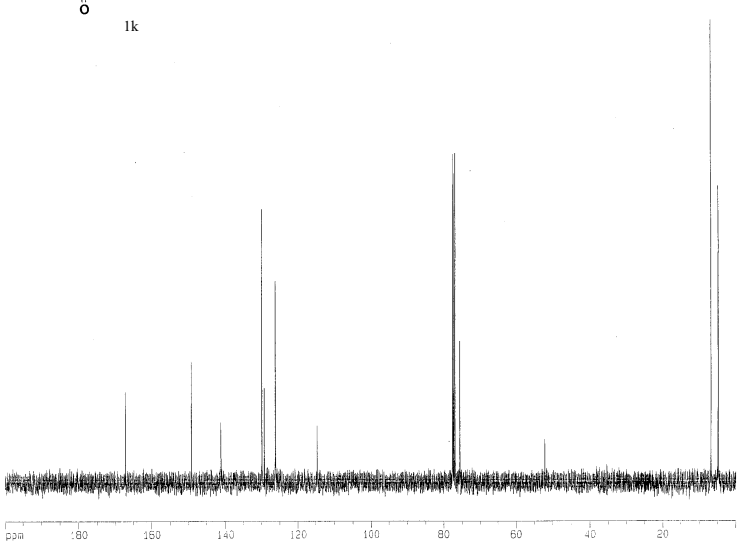
F2 - Processing parameters
SI                         32768
SF                400.1300051 MHz
WDW                           EM
SSB                            0
LB                          0.30 Hz
GB                             0
PC                          1.00

1D NMR plot parameters
CX                         20.00 cm
F1P                       10.000 ppm
F1                      4001.30 Hz
F2P                        0.000 ppm
F2                         0.00 Hz
PPMCM                  0.50000 ppm/cm
HZCM                 200.06500 Hz/cm
```

SN061117



1k




```
Current Data Parameters
NAME            SN1117-C2
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20060403
Time              16.13
INSTRUM           spect
PROBHD    5mm BBO BB-1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   64
DS                    4
SWH           25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG                 2048
DW               19.900 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

========== CHANNEL f1 ==========
NUC1                13C
P1               15.25 usec
PL1               3.00 dB
SFO1        100.6237959 MHz

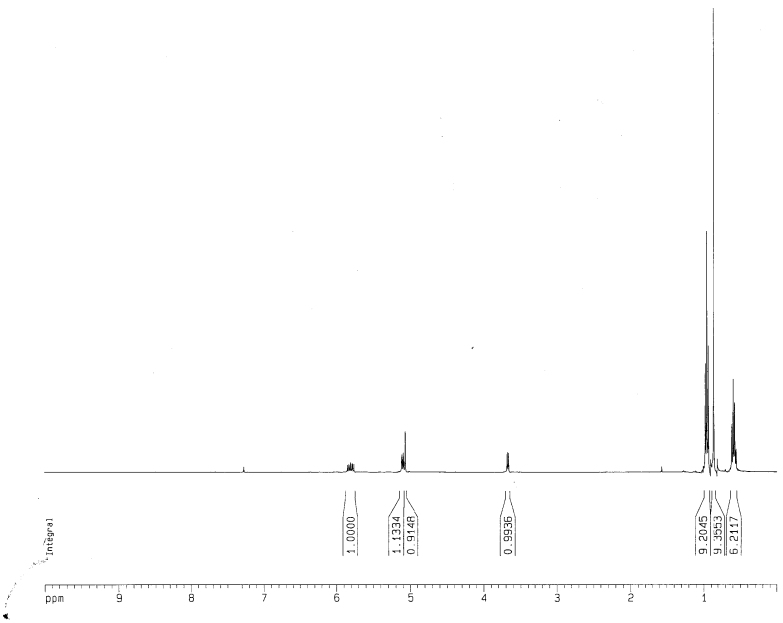
========== CHANNEL f2 ==========
CPDPRG2         waltz16
NUC2                1H
PCPD2           107.50 usec
PL2              0.00 dB
PL12            24.00 dB
PL13            24.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127515 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM          1006.12756 Hz/cm
```

11

SN050733



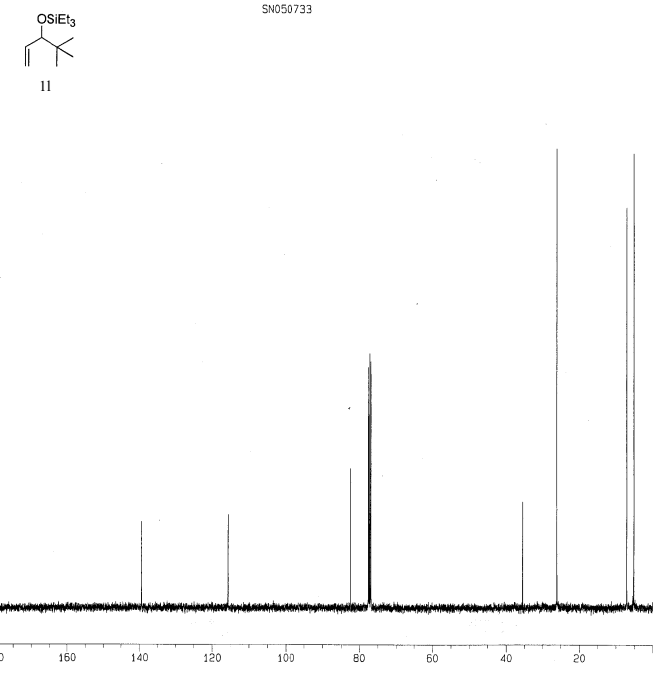

```
Current Data Parameters
NAME            SN733-H
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20050727
Time              22.00
INSTRUM           spect
PROBHD    5mm BBO BB-1
PULPROG           zg30
TD                65536
SOLVENT           CDCl3
NS                    4
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 40.3
DW               60.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec

========== CHANNEL f1 ==========
NUC1                1H
P1                7.90 usec
PL1               0.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1300056 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               10.000 ppm
F1              4001.30 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM          200.06500 Hz/cm
```




```
Current Data Parameters
NAME                SN733-C
EXPNO                     1
PROCNO                    1

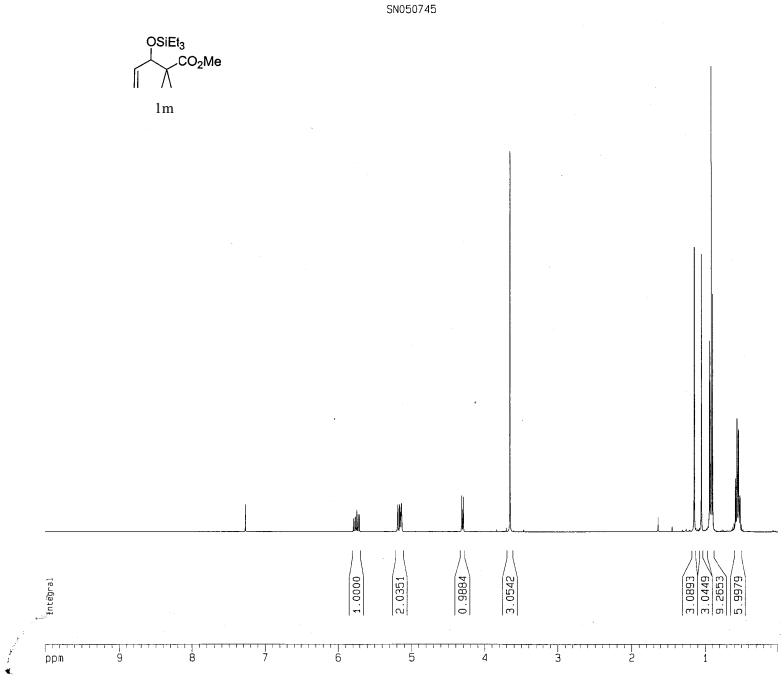
F2 - Acquisition Parameters
Date_            20050727
Time                 22.05
INSTRUM              spect
PROBHD     5mm BBO BB-1
PULPROG           zgpg30
TD                 65536
SOLVENT              CDCl3
NS                     132
DS                       4
SWH            25125.629 Hz
FIDRES          0.383387 Hz
AQ              1.3042164 sec
RG                    4096
DW                19.900 usec
DE                 6.00 usec
TE                300.0 K
D1             2.00000000 sec
d11            0.03000000 sec
d12            0.00002000 sec

========== CHANNEL f1 ==========
NUC1                 13C
P1                15.25 usec
PL1                3.00 dB
SFO1         100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             107.50 usec
PL2                0.00 dB
PL12              24.00 dB
PL13              24.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF           100.6127469 MHz
WDW                     EM
SSB                      0
LB                  1.00 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                200.000 ppm
F1               20122.55 Hz
F2P                  0.000 ppm
F2                   0.00 Hz
PPMCM          10.00000 ppm/cm
HZCM         1006.12744 Hz/cm
```




```
Current Data Parameters
NAME                SN745-H
EXPNO                     1
PROCNO                    1

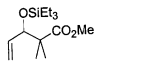
F2 - Acquisition Parameters
Date_            20050801
Time                  5.13
INSTRUM              spect
PROBHD     5mm BBO BB-1
PULPROG              zg30
TD                 65536
SOLVENT              CDCl3
NS                       4
DS                       2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                      64
DW                60.400 usec
DE                 6.00 usec
TE                300.0 K
D1             1.00000000 sec

========== CHANNEL f1 ==========
NUC1                 1H
P1                7.90 usec
PL1                0.00 dB
SFO1         400.1324710 MHz

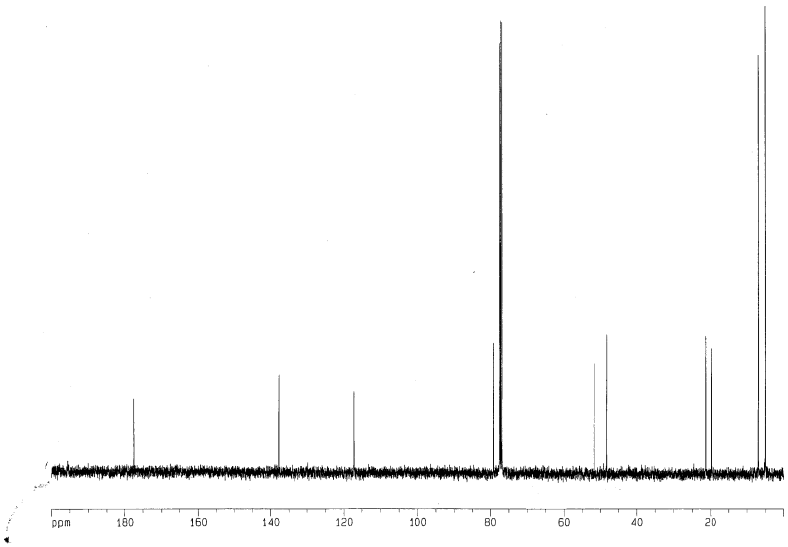
F2 - Processing parameters
SI                   32768
SF           400.1300059 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                  20.00 cm
F1P                10.000 ppm
F1               4001.30 Hz
F2P                  0.000 ppm
F2                   0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM         200.06500 Hz/cm
```

SN050745



1m




```
Current Data Parameters
NAME                  SN745-C
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20050801
Time                    5.22
INSTRUM                 spect
PROBHD     5mm BBO BB-1
PULPROG               zgpg30
TD                     65536
SOLVENT                CDCl3
NS                       150
DS                         4
SWH               25125.629 Hz
FIDRES             0.383397 Hz
AQ                 1.3042164 sec
RG                      4096
DW                    19.900 usec
DE                     6.00 usec
TE                    300.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
d12                0.00002000 sec

========== CHANNEL f1 ==========
NUC1                      13C
P1                      15.25 usec
PL1                      3.00 dB
SFO1             100.5237959 MHz

========== CHANNEL f2 ==========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  107.50 usec
PL2                     0.00 dB
PL12                   24.00 dB
PL13                   24.00 dB
SFO2             400.1316005 MHz

F2 - Processing parameters
SI                       32768
SF                100.5127492 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40

1D NMR plot parameters
CX                       20.00 cm
F1P                     200.000 ppm
F1                    20122.55 Hz
F2P                     0.000 ppm
F2                        0.00 Hz
PPMCM                10.00000 ppm/cm
HZCM               1006.12744 Hz/cm
```

SN061104

1n

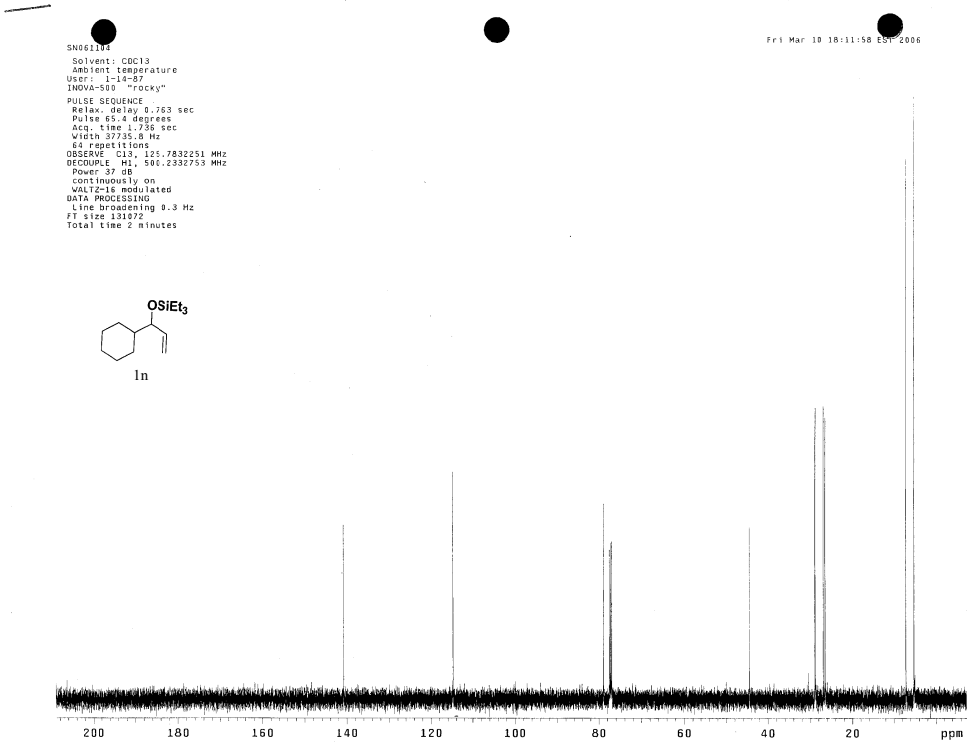

```
Current Data Parameters
NAME                  SN1104-H
EXPNO                       1
PROCNO                      1

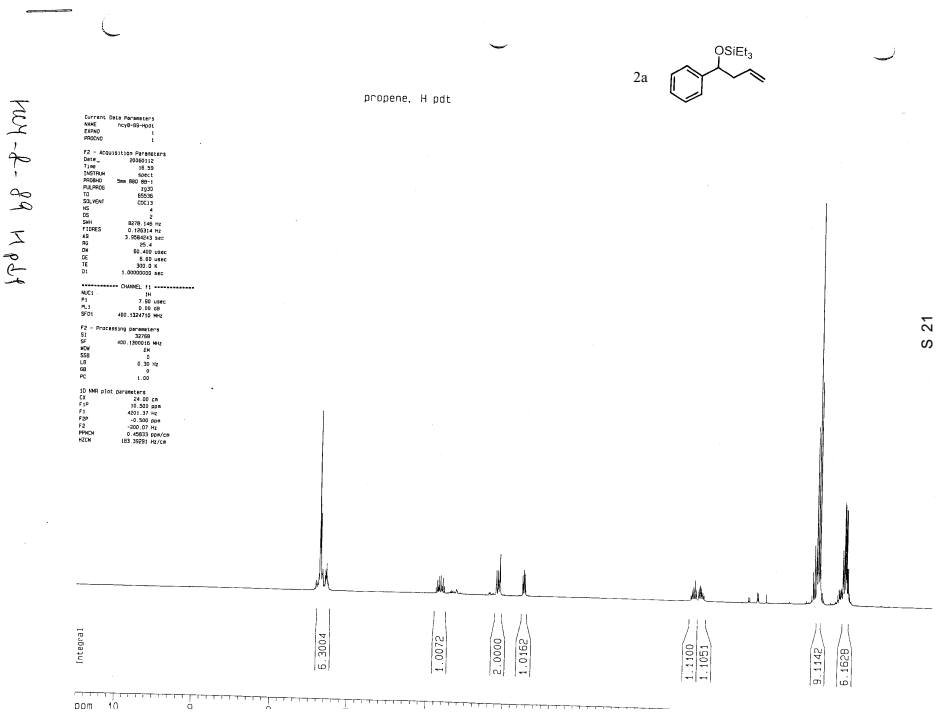
F2 - Acquisition Parameters
Date_              20060310
Time                   12.00
INSTRUM                spect
PROBHD   5 mm QNP  1H/1
PULPROG                zg30
TD                     65536
SOLVENT                CDCl3
NS                         8
DS                         2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9584243 sec
RG                       128
DW                    60.400 usec
DE                     6.00 usec
TE                    292.6 K
D1                 1.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

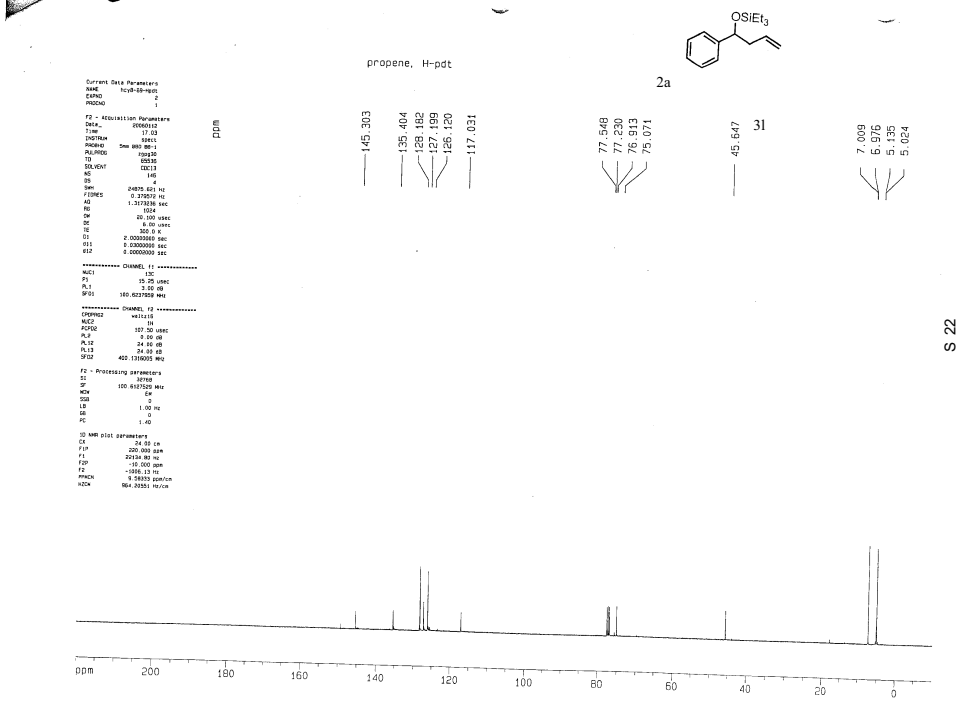
======== CHANNEL f1 ========
NUC1                       1H
P1                      9.88 usec
PL1                      3.00 dB
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                       32768
SF                400.1300054 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00

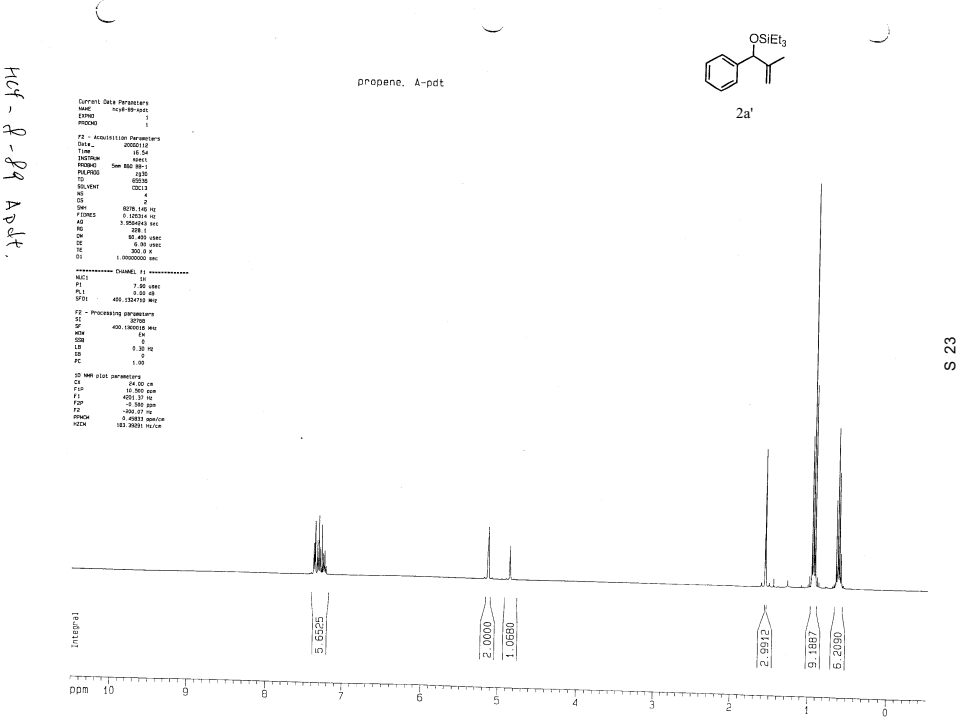
1D NMR plot parameters
CX                       20.00 cm
CY                       12.50 cm
F1P                     10.000 ppm
F1                    4001.30 Hz
F2P                     0.000 ppm
F2                        0.00 Hz
PPMCM                0.50000 ppm/cm
HZCM               200.06500 Hz/cm
```


SN061104
Solvent: CDCl3
Ambient temperature
User: l-14-87
INOVA-500 "rocky"
PULSE SEQUENCE
Relax. delay 0.763 sec
Pulse 65.4 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
64 repetitions
OBSERVE C13, 125.7832251 MHz
DECOUPLE H1, 500.2332753 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 2 minutes
Fri Mar 10 18:11:58 EST 2006
OSiEt3
1n
200
180
160
140
120
100
80
60
40
20
ppm

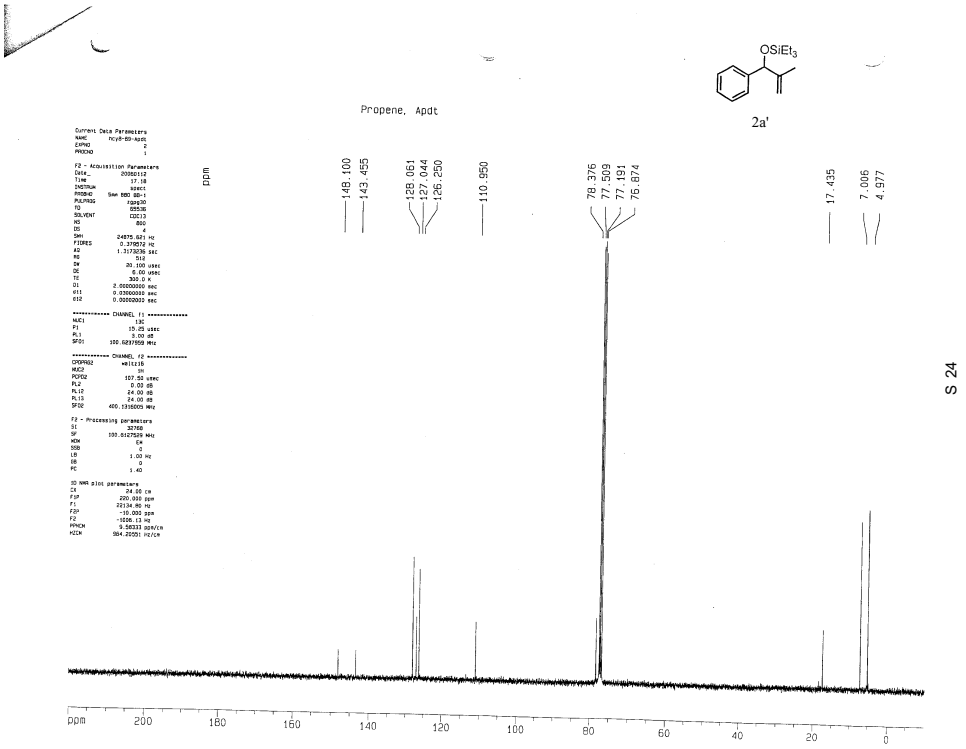

propene, H pdt
2a
OSiEt3
Current Data Parameters
NAME hcy8-09-spot
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060112
Time 18.59
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584245 sec
RG 85.4
DW 60.400 usec
DE 6.50 usec
TE 303.2 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.50 usec
PL1 2.50 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
F1P 10.503 ppm
F1 4201.37 Hz
F2P -0.500 ppm
F2 -200.07 Hz
PPMCM 0.45833 ppm/cm
HZCM 183.39591 Hz/cm
Integral
5.3004
1.0072
2.0000
1.0162
1.1100
1.1051
9.1142
5.1628
ppm
S 21

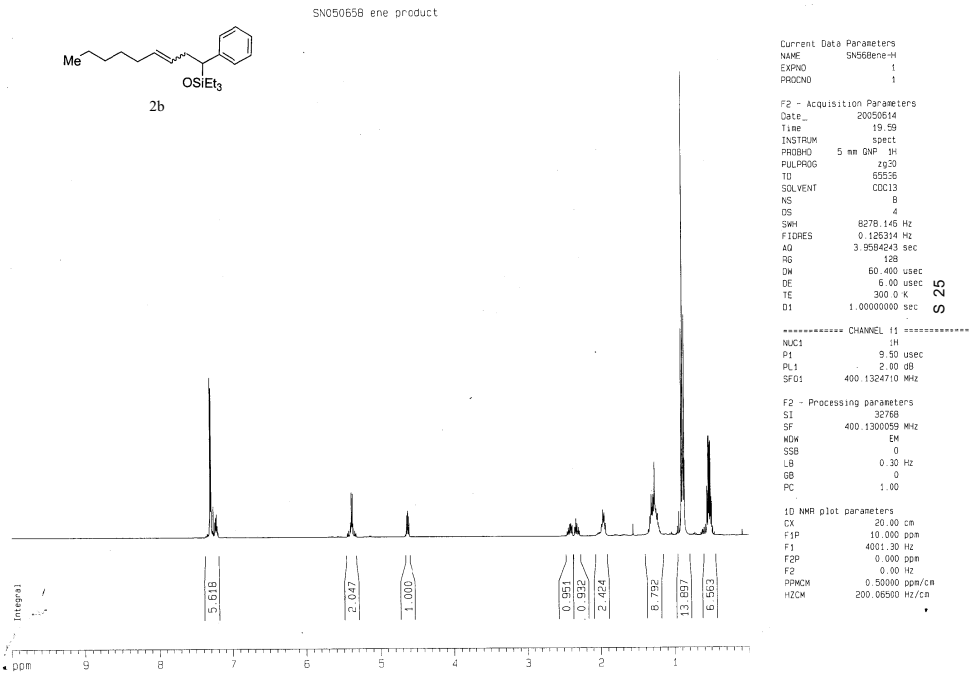

OSiEt3
2a
propene, H-pdt
ppm
145.303
135.404
128.182
127.199
126.120
117.031
77.548
77.230
76.913
75.071
45.647
31
7.009
6.976
5.135
5.024
ppm 200 180 160 140 120 100 80 60 40 20 0

S 22

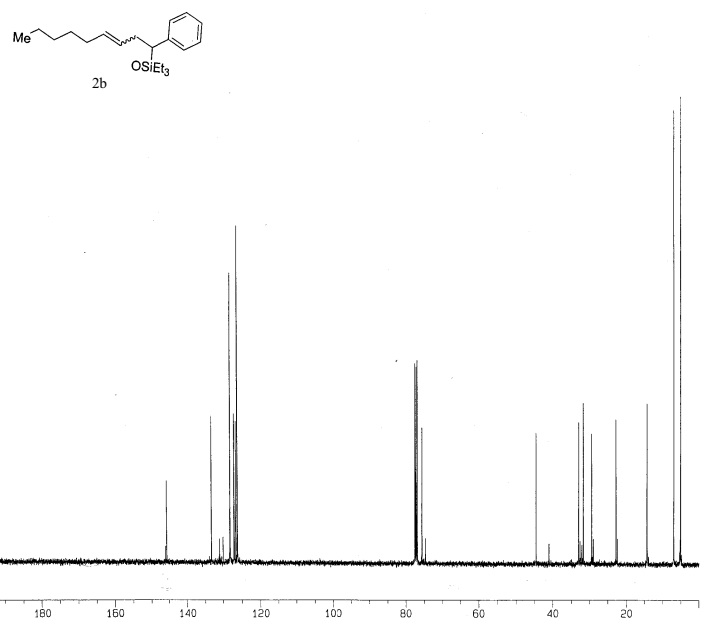

OSiEt3
2a'
propene, A-pdt
integral
5.6525
2.0000
1.0680
2.9912
9.1887
6.2090
ppm 10 9 8 7 6 5 4 3 2 1 0

S 23


OSiEt3
Propene, Apdt
2a'
ppm
148.100
143.455
128.061
127.044
126.250
110.950
78.376
77.509
77.191
76.874
17.435
7.006
4.977
S 24


SN050658 ene product
Me
OSiEt3
2b
Current Data Parameters
NAME SN560ene-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050614
Time 19.59
INSTRUM spect
PROBHD 5 mm GNP 1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 4
SWH 8278.145 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 128
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 9.50 usec
PL1 2.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300059 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm
Integral
5.618
2.047
1.000
0.951
0.932
2.424
8.732
13.897
6.563
ppm
S 25

octene benzaldehyde TESOTf ene




```
Current Data Parameters
NAME       octene-ene-C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20050716
Time               22.11
INSTRUM            spect
PROBHD     5mm BBC BB-1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  213
DS                    4
SWH           25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG                1149.4
DW               19.900 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

========== CHANNEL f1 ==========
NUC1                 13C
P1                 15.25 usec
PL1                 3.00 dB
SFO1         100.6237959 MHz

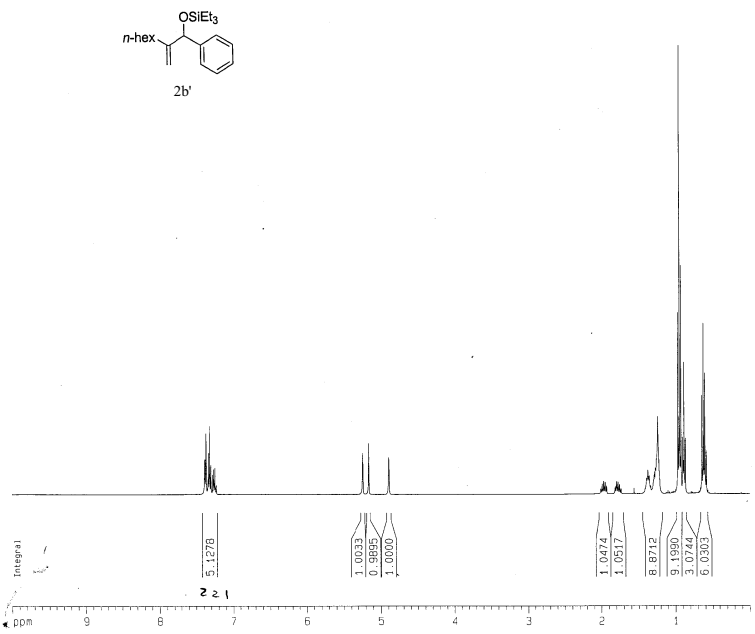
========== CHANNEL f2 ==========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              107.50 usec
PL2                 0.00 dB
PL12               24.00 dB
PL13               24.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF           100.6127476 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
F1P               200.000 ppm
F1              20122.55 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          10.00000 ppm/cm
HZCM         1006.12744 Hz/cm
```

S26

SN050658 allylic alcohol



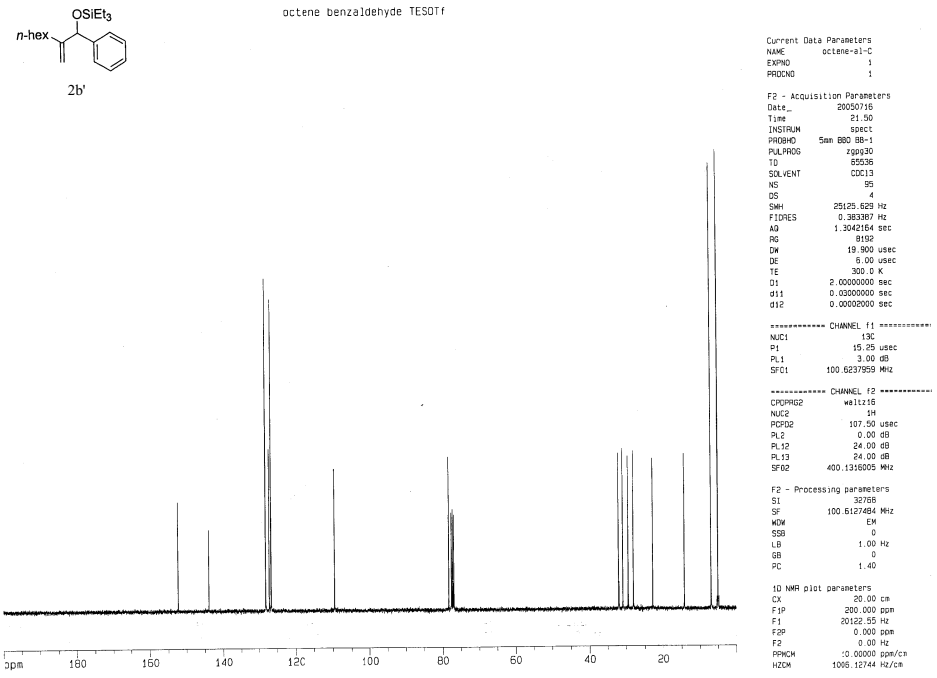

```
Current Data Parameters
NAME        SN658heck-c
EXPNO                 1
PROCNO                1

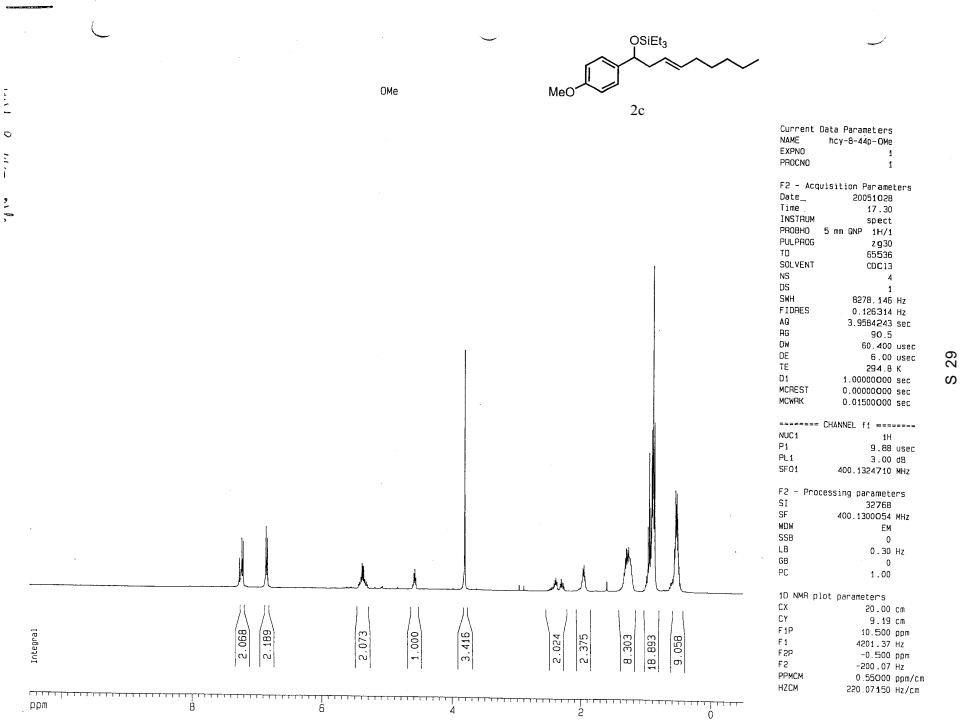
F2 - Acquisition Parameters
Date_          20050614
Time               19.05
INSTRUM            spect
PROBHD     5 mm QNP  1H
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    4
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                   64
DW               60.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec

========== CHANNEL f1 ==========
NUC1                 1H
P1                 9.50 usec
PL1                2.00 dB
SFO1         400.1324710 MHz

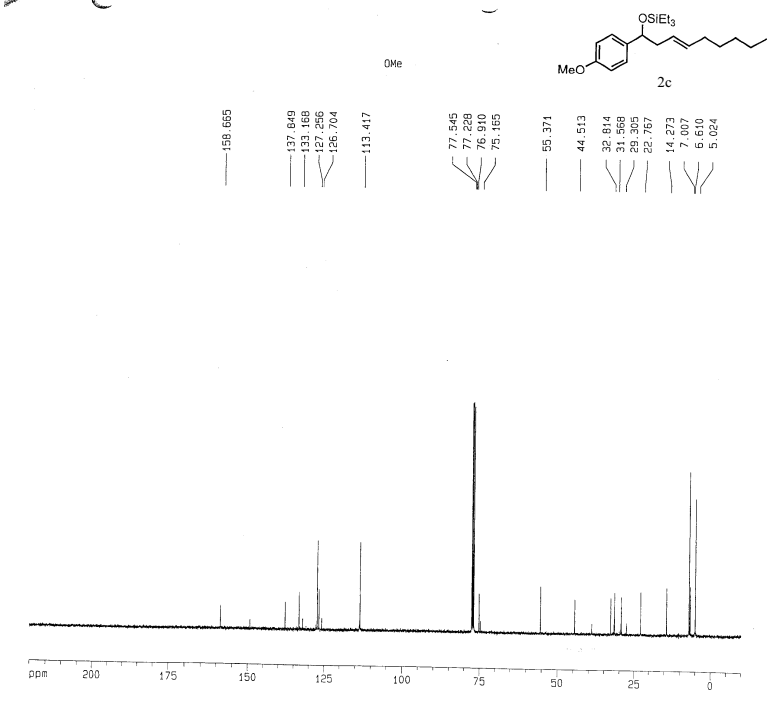
F2 - Processing parameters
SI                  32768
SF           400.1300000 MHz
WDW                    EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P                10.000 ppm
F1              4001.30 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM         200.06500 Hz/cm
```


OSiEt3
n-hex
2b'
octene benzaldehyde TESOTf
Current Data Parameters
NAME octene-al-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050716
Time 21.50
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 95
DS 4
SWH 25125.629 Hz
FIDRES 0.383387 Hz
AQ 1.3042164 sec
RG 8192
DW 19.900 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127484 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 200.000 ppm
F1 20122.55 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.00000 ppm/cm
HZCM 1006.12744 Hz/cm
ppm
180
160
140
120
100
80
60
40
20


OMe
OSiEt3
MeO
2c
Current Data Parameters
NAME hcy-6-44p-OMe
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051028
Time 17.30
INSTRUM spect
PROBHD 5 mm GNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 1
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 90.5
DW 60.400 usec
DE 6.00 usec
TE 294.8 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 9.19 cm
F1P 10.500 ppm
F1 4201.37 Hz
F2P -0.500 ppm
F2 -200.07 Hz
PPMCM 0.59000 ppm/cm
HZCM 220.07150 Hz/cm
Integral
2.068
2.189
2.073
1.000
3.416
2.024
2.375
8.303
18.693
9.056
ppm
8
6
4
2
0

S 29




```
Current Data Parameters
NAME        hcy-B-44-OMe
EXPNO               2
PROCNO              1

F2 - Acquisition Parameters
Date_         20051028
Time            16.05
INSTRUM         spect
PROBHD   5mm BBO BB-1
PULPROG         zgpg30
TD              65536
SOLVENT         CDCl3
NS              1024
DS                4
SWH         24875.621 Hz
FIDRES       0.379572 Hz
AQ          1.3173236 sec
RG              1024
DW           20.100 usec
DE            6.00 usec
TE             300.0 K
D1          2.00000000 sec
d11         0.03000000 sec
d12         0.00002000 sec

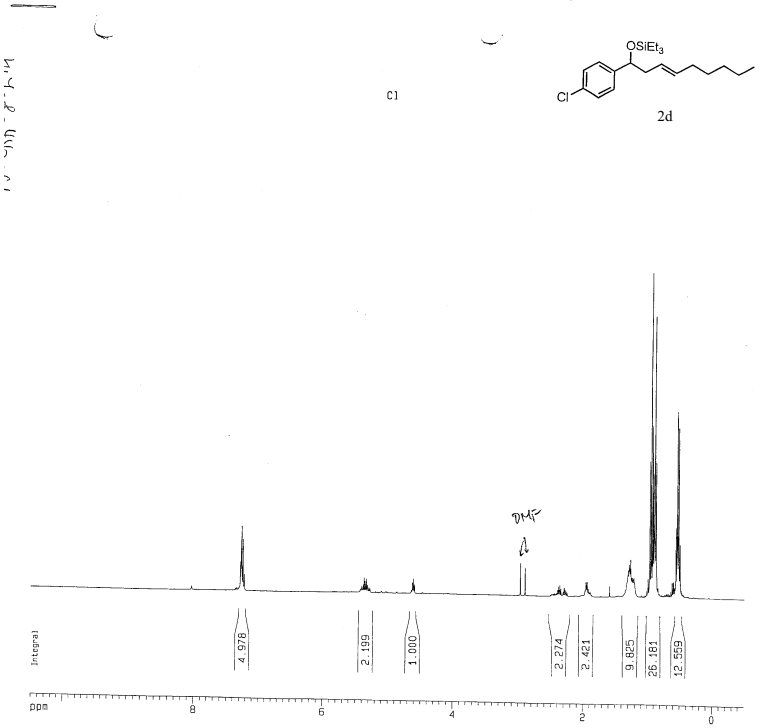
========== CHANNEL f1 ==========
NUC1              13C
P1              15.25 usec
PL1             3.00 dB
SFO1      100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2         waltz16
NUC2              1H
PCPD2          107.50 usec
PL2             0.00 dB
PL12           24.00 dB
PL13           24.00 dB
SFO2      400.1316005 MHz

F2 - Processing parameters
SI              32768
SF        100.6127499 MHz
WDW               EM
SSB               0
LB             1.00 Hz
GB                0
PC             1.40

1D NMR plot parameters
CX             20.00 cm
F1P          220.000 ppm
F1         22134.80 Hz
F2P          -10.000 ppm
F2         -1005.13 Hz
PPMCM        11.50000 ppm/cm
HZCM       1157.04563 Hz/cm
```

S 30




```
Current Data Parameters
NAME        hcy-B-44p-Cl
EXPNO               1
PROCNO              1

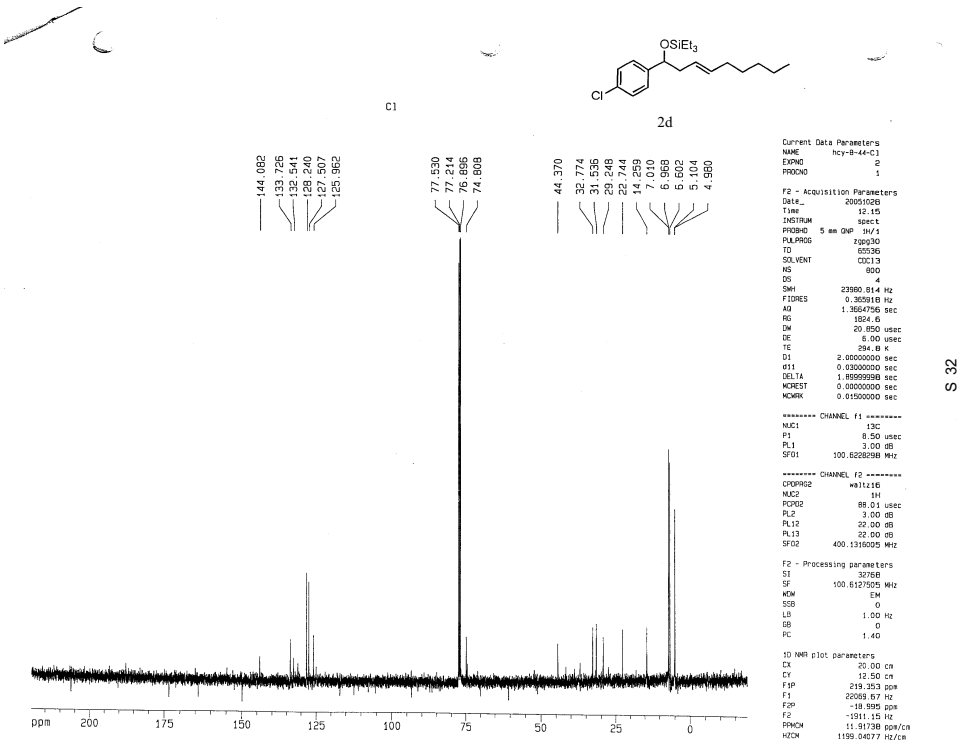
F2 - Acquisition Parameters
Date_         20051028
Time            17.34
INSTRUM         spect
PROBHD   5 mm QNP  1H/1
PULPROG         zg30
TD              65536
SOLVENT         CDCl3
NS                8
DS                1
SWH          8278.145 Hz
FIDRES       0.126314 Hz
AQ          3.9584243 sec
RG              50.5
DW           60.400 usec
DE            6.00 usec
TE             294.8 K
D1          1.00000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

========= CHANNEL f1 =========
NUC1              1H
P1              9.88 usec
PL1             3.00 dB
SFO1      400.1324710 MHz

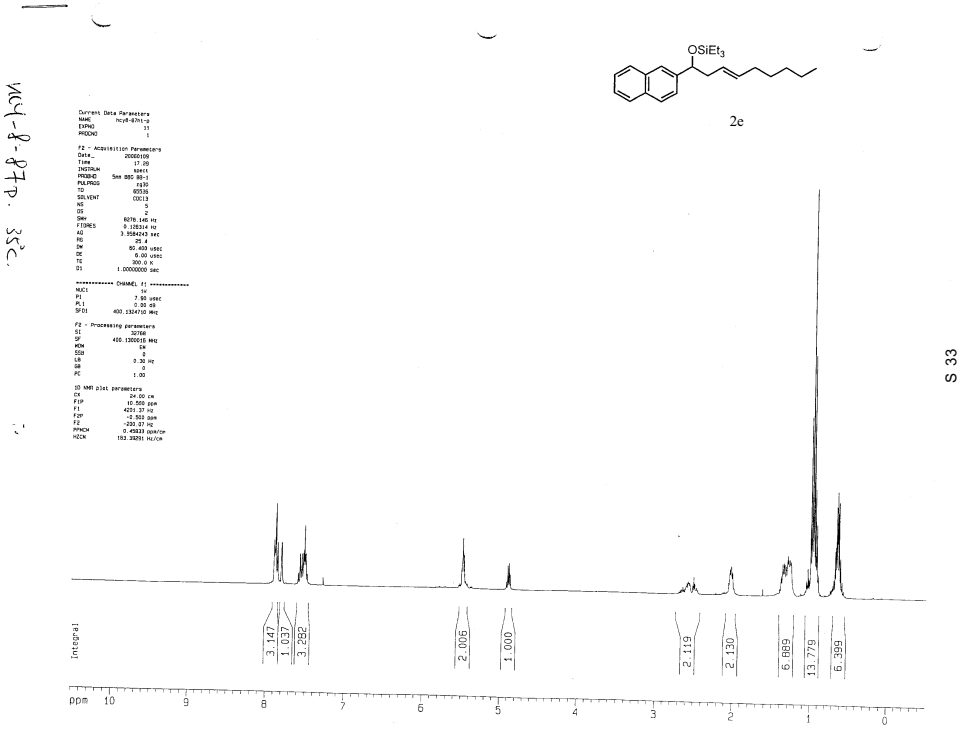
F2 - Processing parameters
SI              32768
SF        400.1300054 MHz
WDW               EM
SSB               0
LB             0.30 Hz
GB                0
PC             1.00

1D NMR plot parameters
CX             20.00 cm
CY              9.19 cm
F1P          10.500 ppm
F1         4201.37 Hz
F2P          -0.500 ppm
F2         -200.07 Hz
PPMCM         0.55000 ppm/cm
HZCM       220.07150 Hz/cm
```

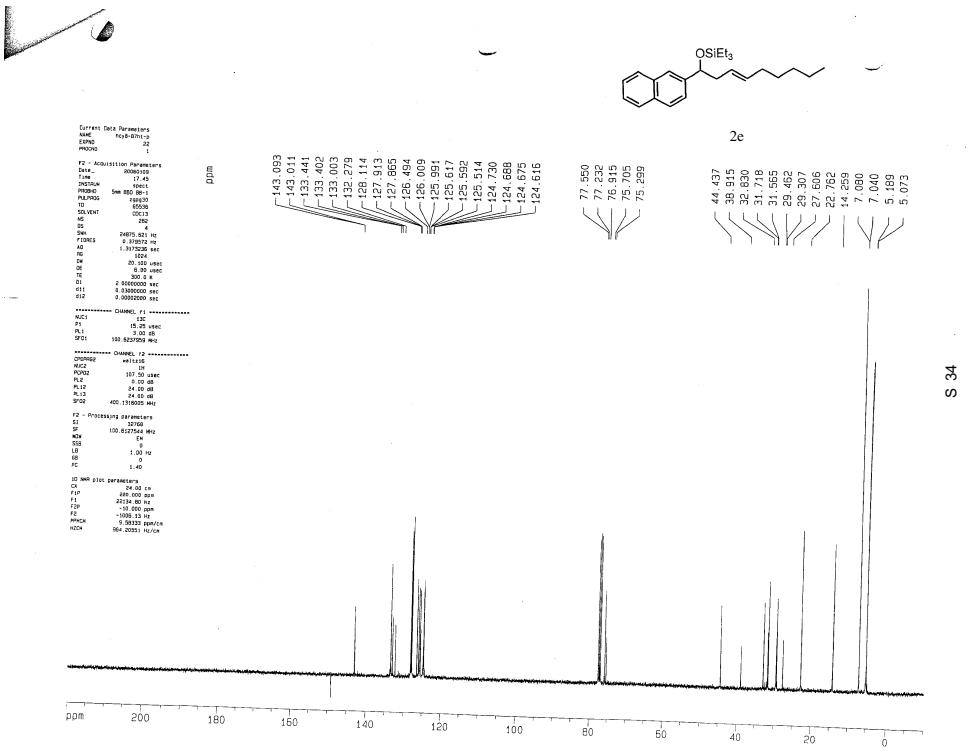
S 31


OSiEt3
Cl
2d
144.082
133.726
132.541
128.240
127.507
125.962
77.530
77.214
76.896
74.808
44.370
32.774
31.536
29.248
22.744
14.259
7.010
6.968
6.602
5.104
4.980
ppm 200 175 150 125 100 75 50 25 0
Current Data Parameters
NAME hcy-8-44-C1
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091026
Time 12.15
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 800
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 1824.6
DW 20.850 usec
DE 6.00 usec
TE 294.8 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 3.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 88.01 usec
PL2 3.00 dB
PL12 22.00 dB
PL13 22.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127505 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 219.353 ppm
F1 22069.67 Hz
F2P -19.995 ppm
F2 -1911.15 Hz
PPMCM 11.91738 ppm/cm
HZCM 1199.04077 Hz/cm

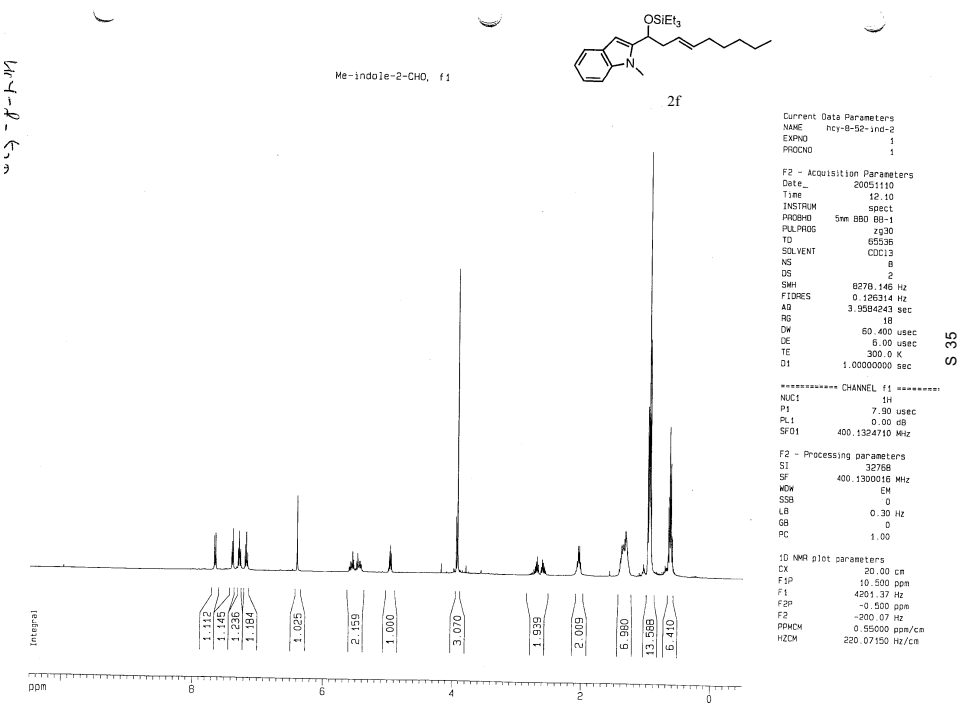
S 32


OSiEt3
2e
Integral
3.147
1.037
3.282
2.006
1.000
2.119
2.130
6.889
13.779
6.399
ppm 10 9 8 7 6 5 4 3 2 1 0

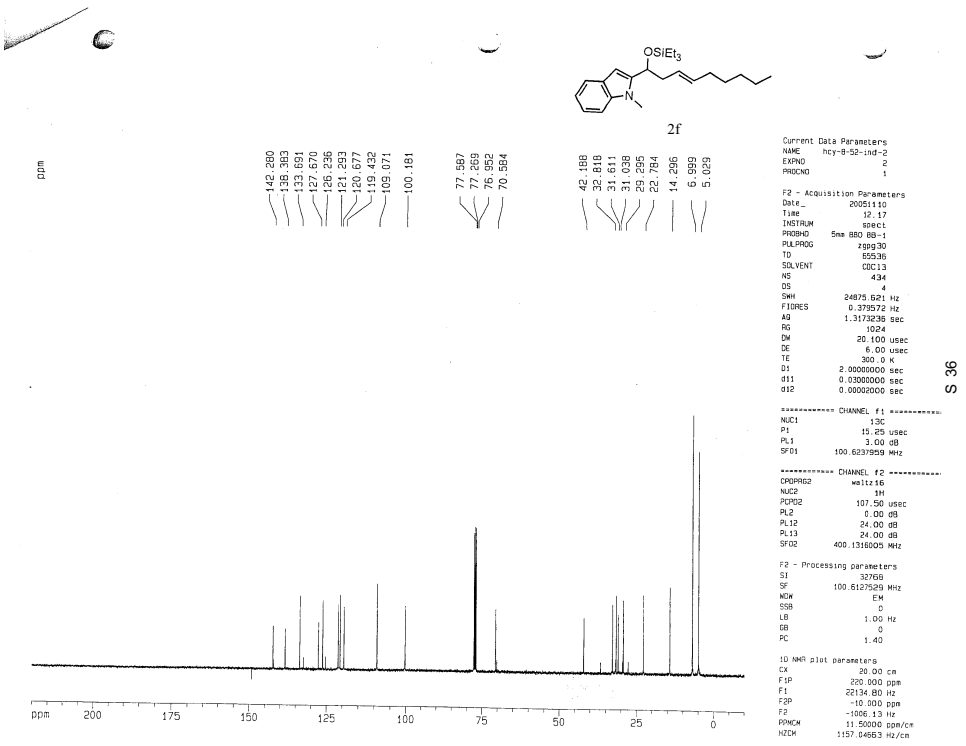
S 33


OSiEt3
2e
Current Data Parameters
NAME hcy-8-07h1-p
EXPNO 22
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080109
Time 17.45
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 352
DS 4
SWH 24875.621 Hz
FIDRES 0.379572 Hz
AQ 1.3173226 sec
RG 1024
DW 20.100 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237259 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127544 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 24.00 cm
F1P 185.000 ppm
F1 22134.80 Hz
F2P -10.000 ppm
F2 -1030.13 Hz
PPMCM 9.58333 ppm/cm
HZCM 964.20551 Hz/cm
143.093
143.011
133.441
133.402
133.003
132.279
128.114
127.913
127.865
126.494
126.009
125.991
125.617
125.592
125.514
124.730
124.688
124.675
124.616
77.550
77.232
76.915
75.705
75.299
44.437
38.915
32.830
31.718
31.565
29.462
29.307
27.606
22.762
14.259
7.080
7.040
5.189
5.073
ppm
200
180
160
140
120
100
80
60
40
20
0

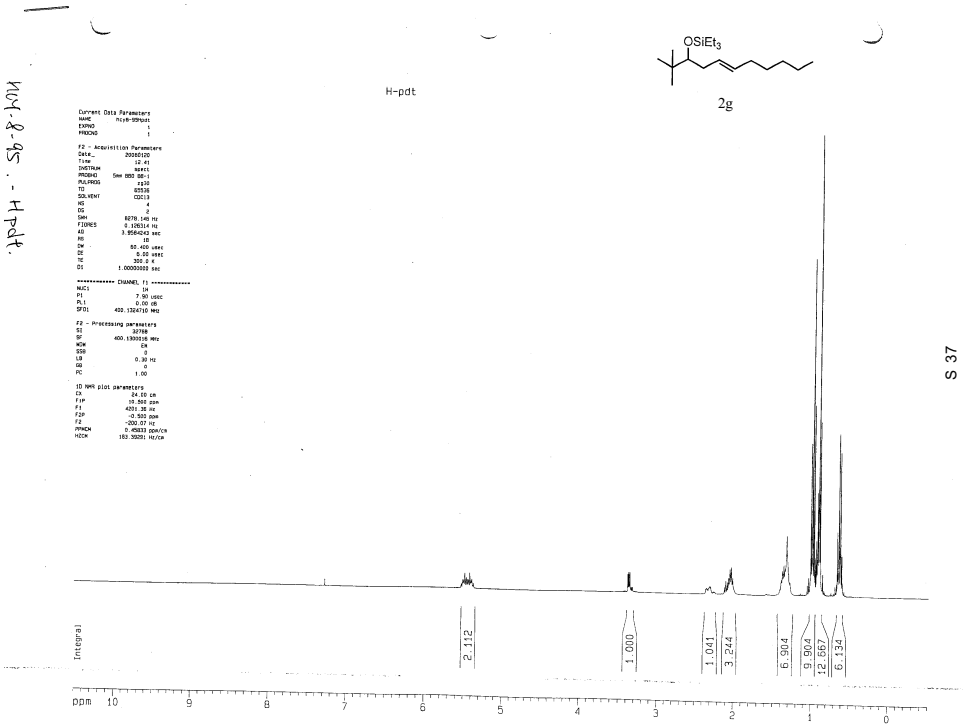
S 34


OSiEt3
2f
Me-indole-2-CHO, f1
Current Data Parameters
NAME hcy-8-52-ind-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051110
Time 12.10
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 18
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300016 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.500 ppm
F1 4201.37 Hz
F2P -0.500 ppm
F2 -200.07 Hz
PPMCM 0.55000 ppm/cm
HZCM 220.07150 Hz/cm
Integral
1.112
1.145
1.236
1.184
1.025
2.159
1.000
3.070
1.939
2.009
6.980
13.588
6.410
ppm
8
6
4
2
0

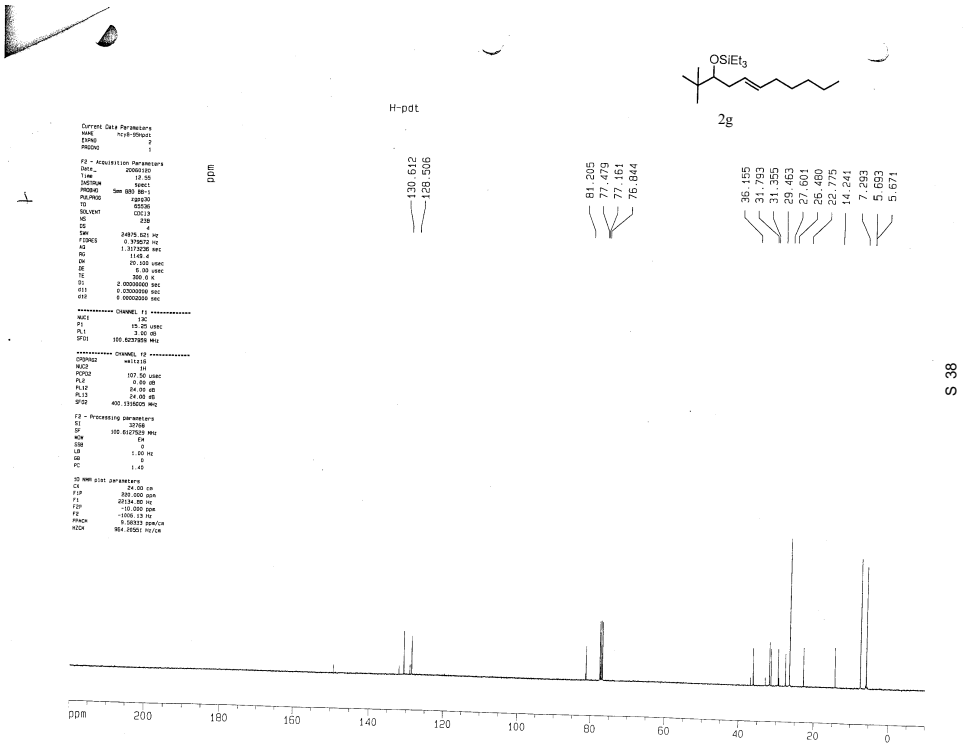
S 35


OSiEt3
N
2f
ppm
142.280
138.383
133.691
127.670
126.236
121.293
120.677
119.432
109.071
100.181
77.587
77.269
76.952
70.584
42.188
32.818
31.611
31.038
29.295
22.784
14.296
6.999
5.029
Current Data Parameters
NAME hcy-8-52-ind-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051110
Time 12.17
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 434
DS 4
SWH 24875.621 Hz
FIDRES 0.379572 Hz
AQ 1.3173236 sec
RG 1024
DW 20.100 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
DECPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127529 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 220.000 ppm
F1 22134.80 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 11.50000 ppm/cm
HZCM 1157.04663 Hz/cm
ppm 200 175 150 125 100 75 50 25 0

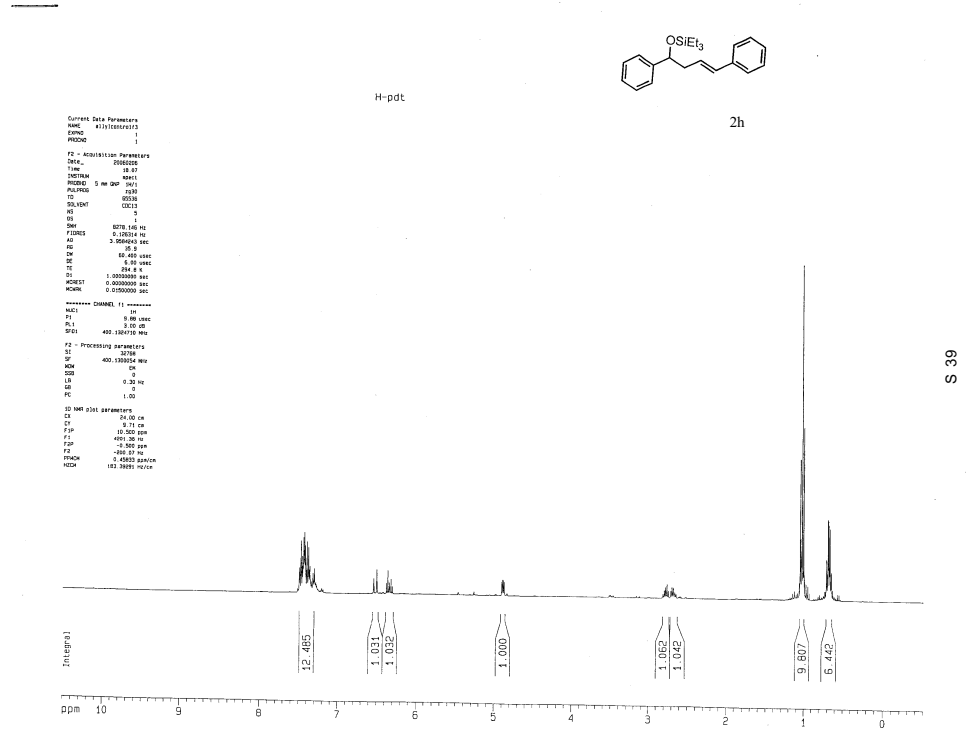
S 36


OSiEt3
2g
H-pdt
Current Data Parameters
NAME hcy8-95hpdt
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060120
Time 12.41
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9564243 sec
RG 16
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
CHANNEL f1
NUC1 1H
P1 7.50 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300018 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 24.00 cm
F1P 10.500 ppm
F1 4201.20 Hz
F2P -0.500 ppm
F2 -200.07 Hz
PPMCM 0.45833 ppm/cm
HZCM 183.35281 Hz/cm
Integral
2.112
1.000
1.041
3.244
6.904
9.904
12.667
6.134
ppm 10 9 8 7 6 5 4 3 2 1 0

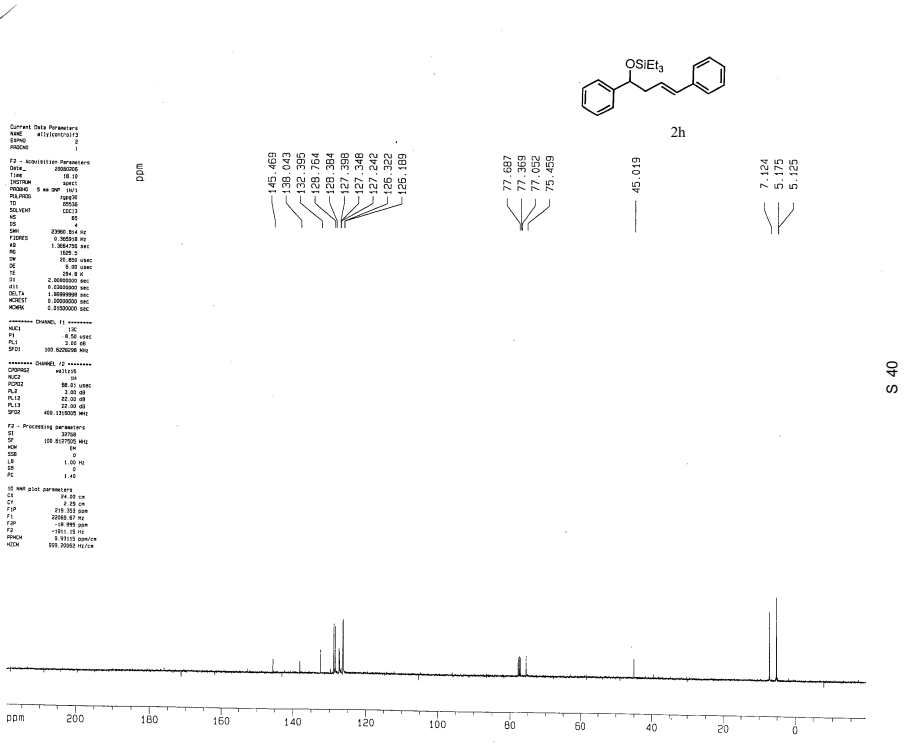
S 37


OSiEt3
2g
H-pdt
ppm
130.612
128.506
81.205
77.479
77.161
76.844
36.155
31.793
31.355
29.463
27.601
26.480
22.775
14.241
7.293
5.693
5.671
ppm 200 180 160 140 120 100 80 60 40 20 0

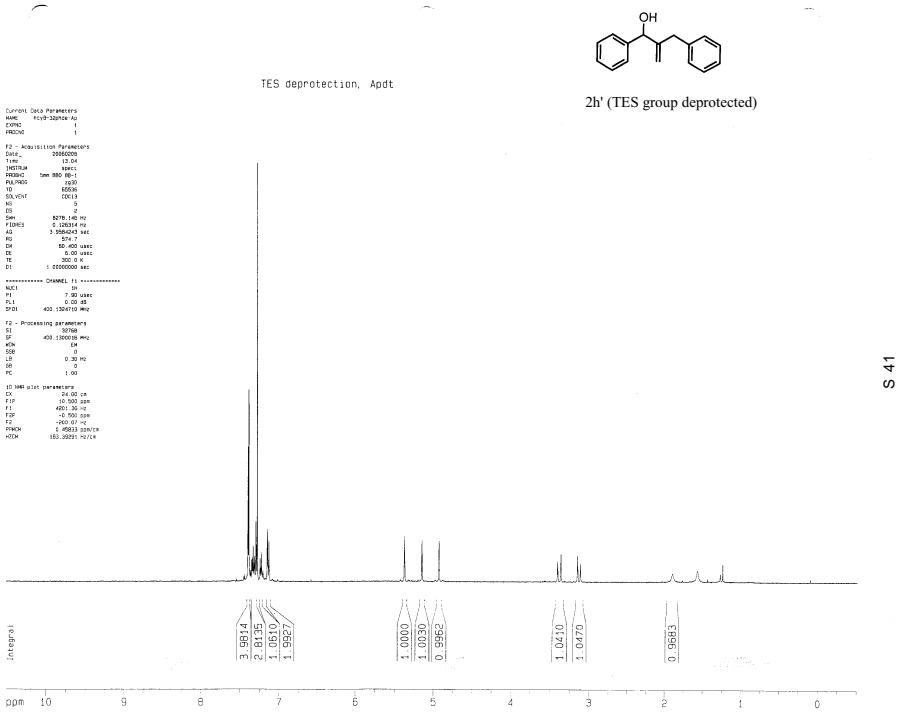
S 38


OSiEt3
2h
H-pdt
Integral
12.485
1.031
1.032
1.000
1.062
1.042
9.807
6.442
ppm 10 9 8 7 6 5 4 3 2 1 0

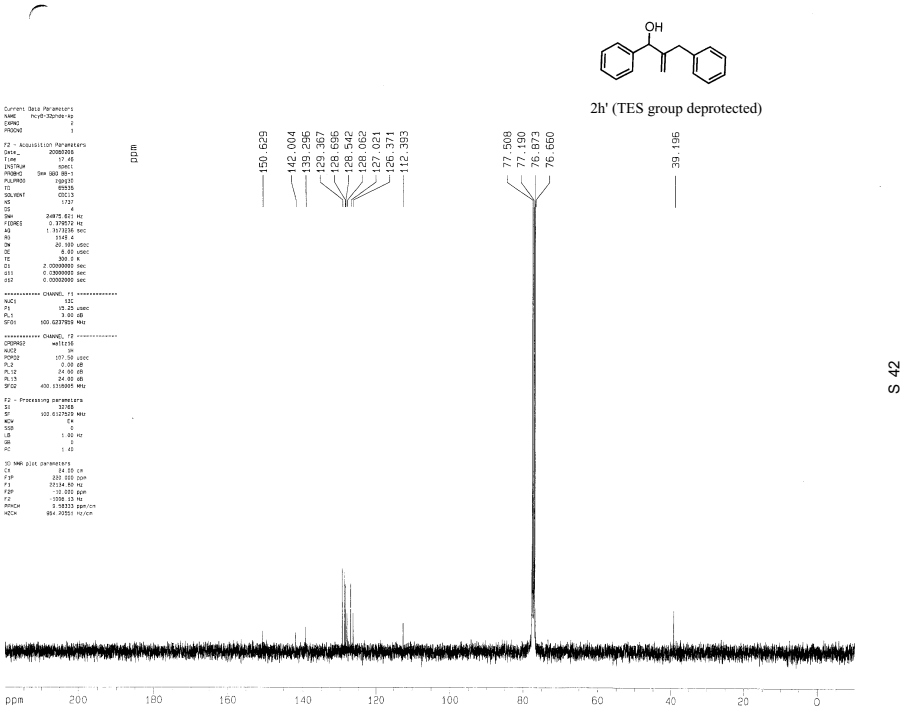
S 39


OSiEt3
2h
145.469
138.043
132.395
128.764
128.384
127.398
127.348
127.242
126.322
126.189
77.687
77.369
77.052
75.459
45.019
7.124
5.175
5.125
ppm
200
180
160
140
120
100
80
60
40
20
0

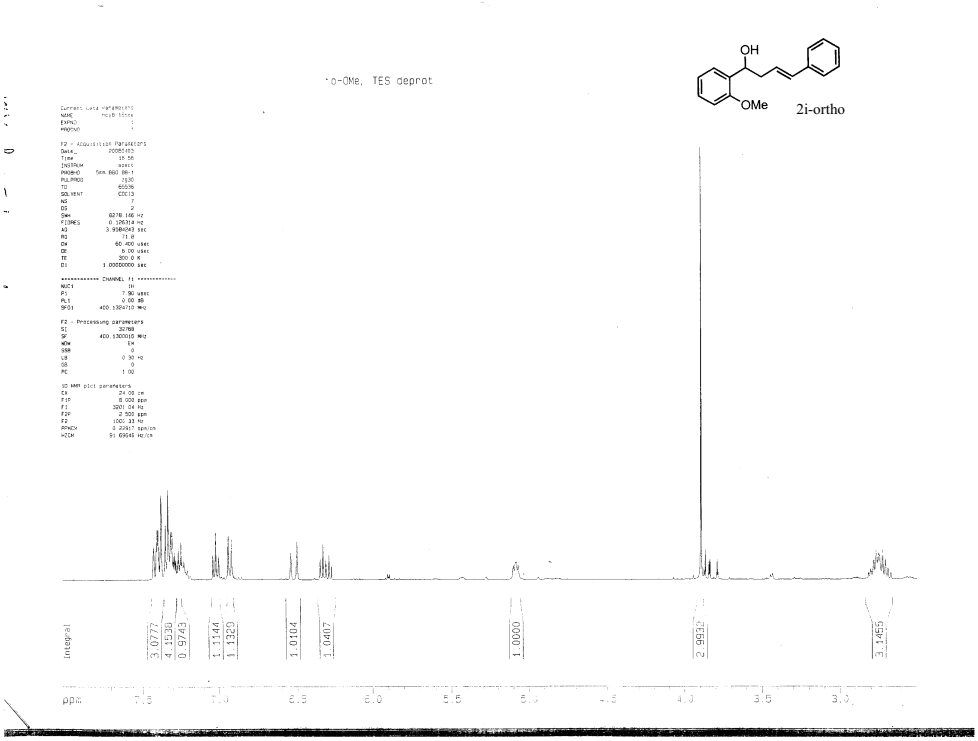
S 40

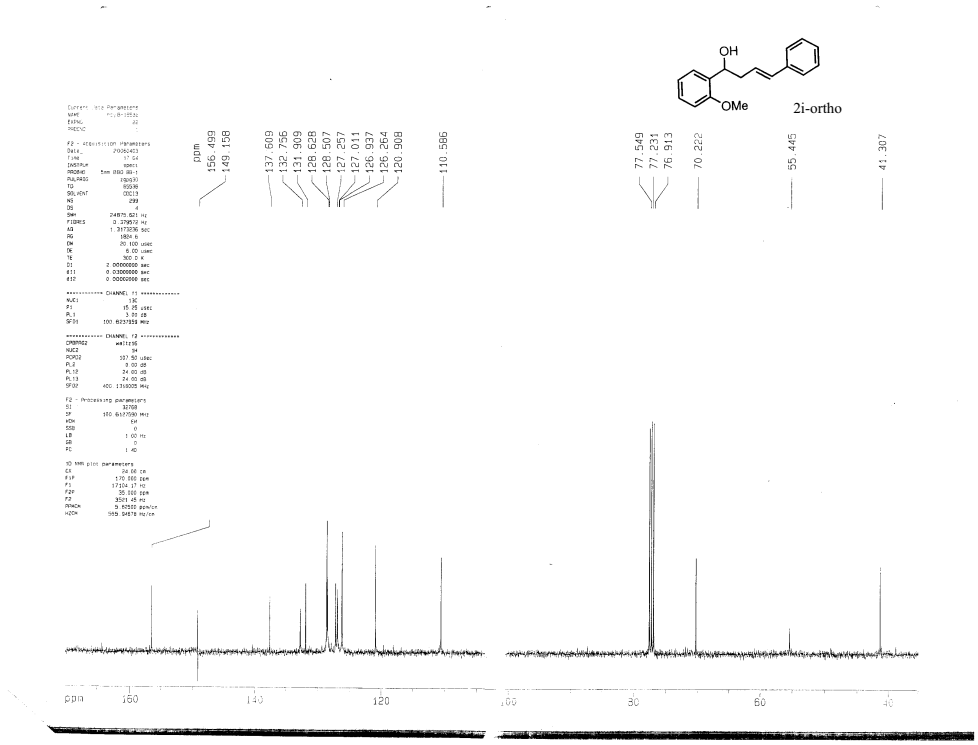

OH
2h' (TES group deprotected)
TES deprotection, Apdt
3.9814
2.8135
1.0610
1.9927
1.0000
1.0030
0.9962
1.0410
1.0470
0.9683
Integral
ppm
10
9
8
7
6
5
4
3
2
1
0

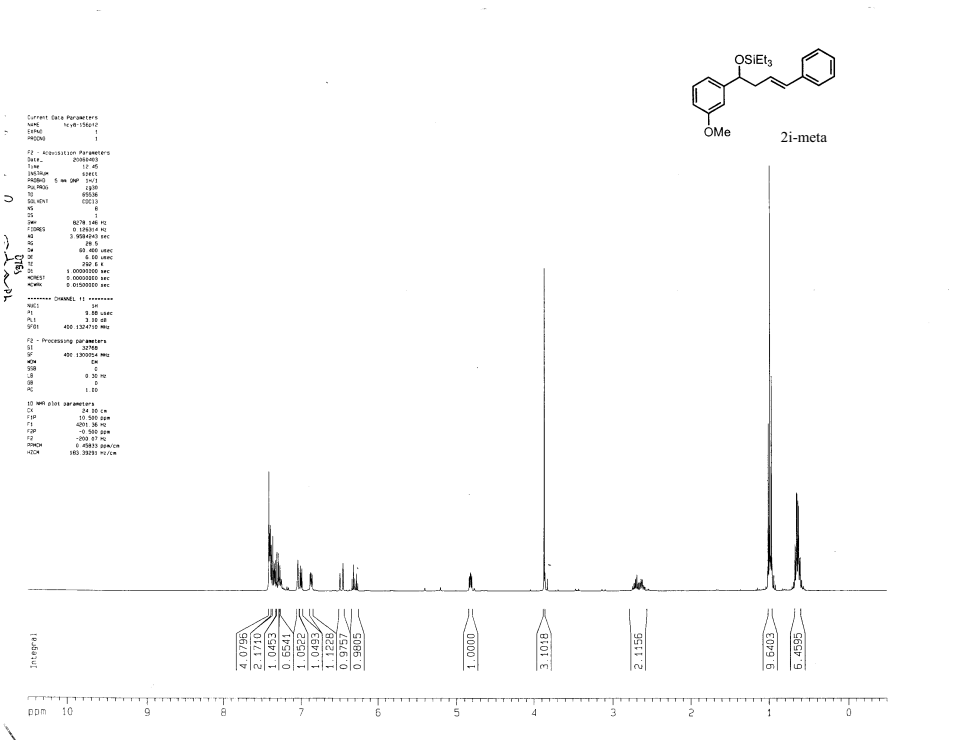
S 41

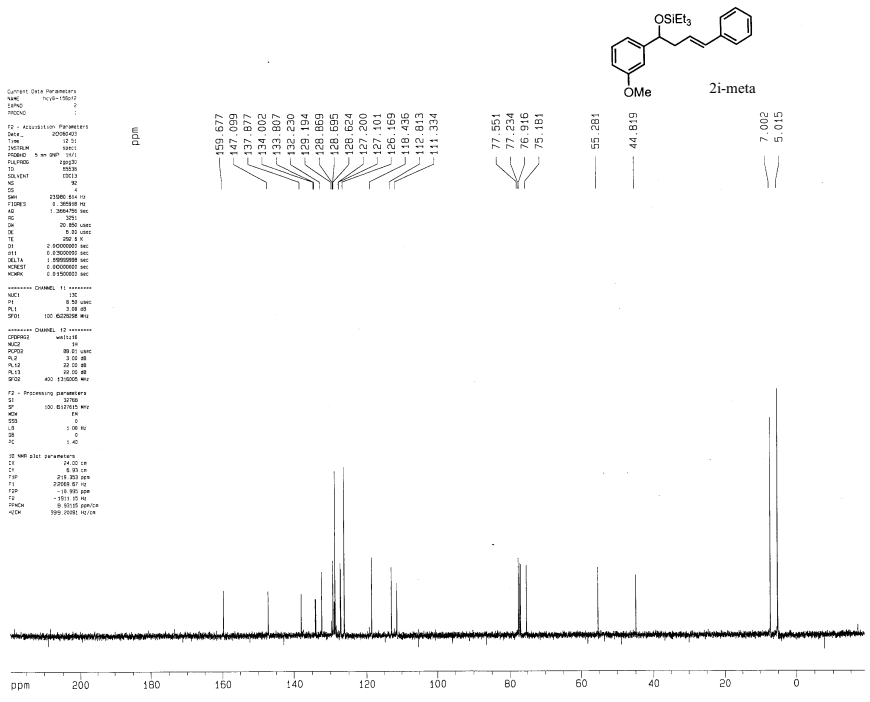

OH
2h' (TES group deprotected)
ppm
150.629
142.004
139.296
129.367
128.696
128.542
128.062
127.021
126.371
112.393
77.508
77.190
76.873
76.660
39.196
ppm 200 180 160 140 120 100 80 60 40 20 0

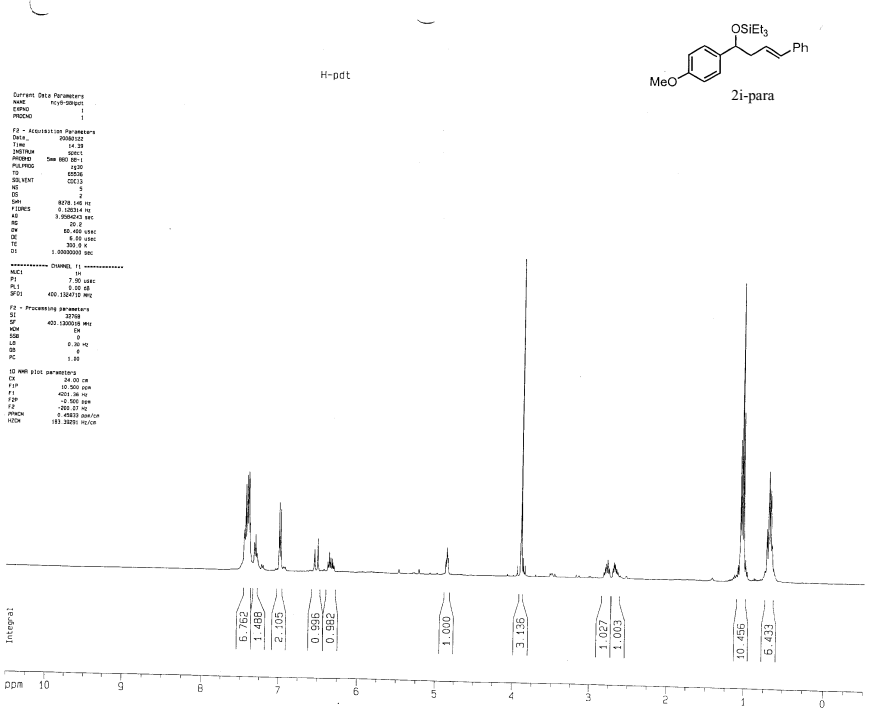
S 42


OH
OMe
2i-ortho
integral
3.0777
4.1536
0.5743
1.1144
1.1320
1.0104
1.0407
1.0000
2.9938
3.1465
ppm 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0

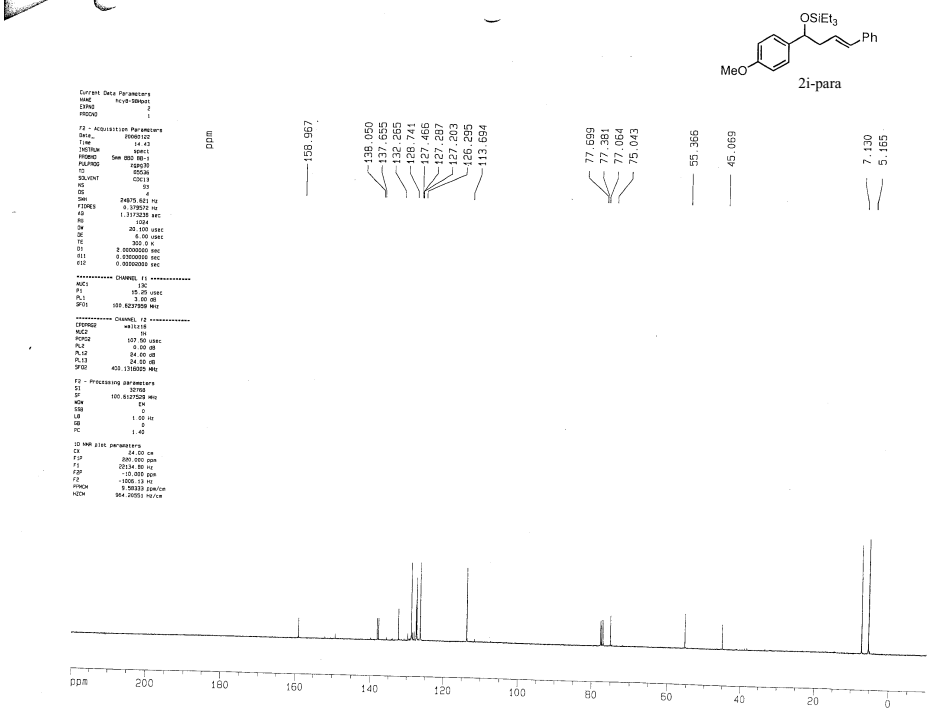

OH
OMe
2i-ortho
ppm
156.499
149.158
137.609
132.756
131.909
128.628
128.507
127.257
127.011
126.937
126.264
120.908
110.586
77.549
77.231
76.913
70.222
55.445
41.307
ppm 160 140 120 100 80 60 40


OSiEt3
OMe
2i-meta
Integral
4.0796
2.1710
1.0453
0.6541
1.0522
1.0493
1.1228
0.9757
0.9805
1.0000
3.1018
2.1156
9.6403
6.4595
ppm 10 9 8 7 6 5 4 3 2 1 0

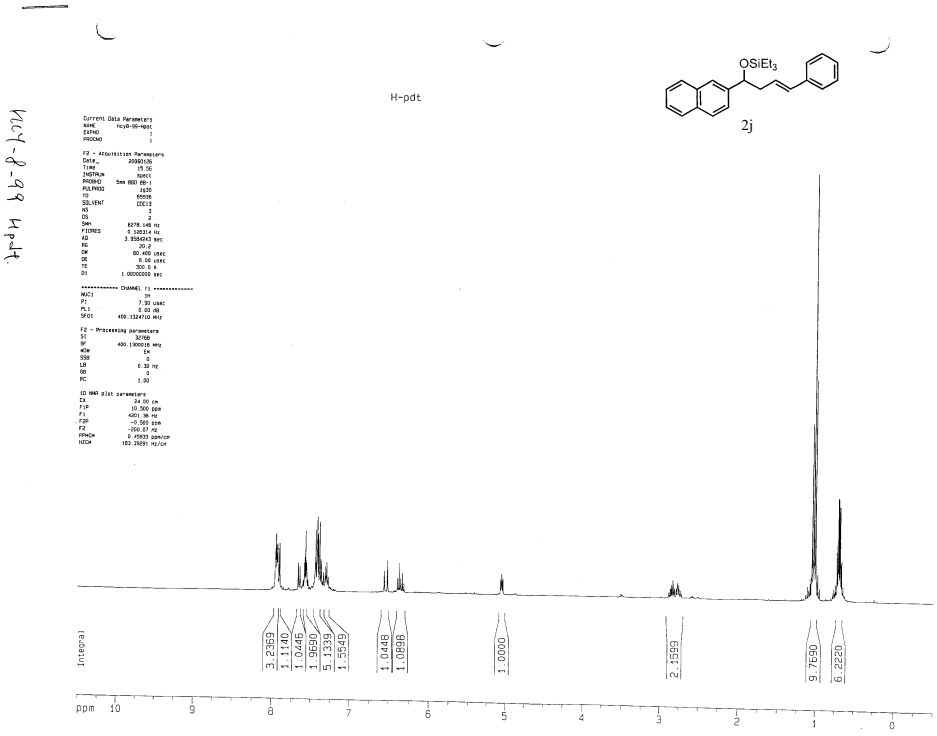

OSiEt3
OMe
2i-meta
ppm
159.677
147.099
137.877
134.002
133.807
132.230
129.194
128.869
128.695
128.624
127.200
127.101
126.169
118.435
112.813
111.334
77.551
77.234
76.916
75.181
55.281
44.819
7.002
5.015
ppm 200 180 160 140 120 100 80 60 40 20 0


OSiEt3
Ph
MeO
2i-para
H-pdt
Integral
6.762
1.488
2.105
0.996
0.982
1.000
3.136
1.027
1.003
10.456
6.433
ppm 10 9 8 7 6 5 4 3 2 1 0

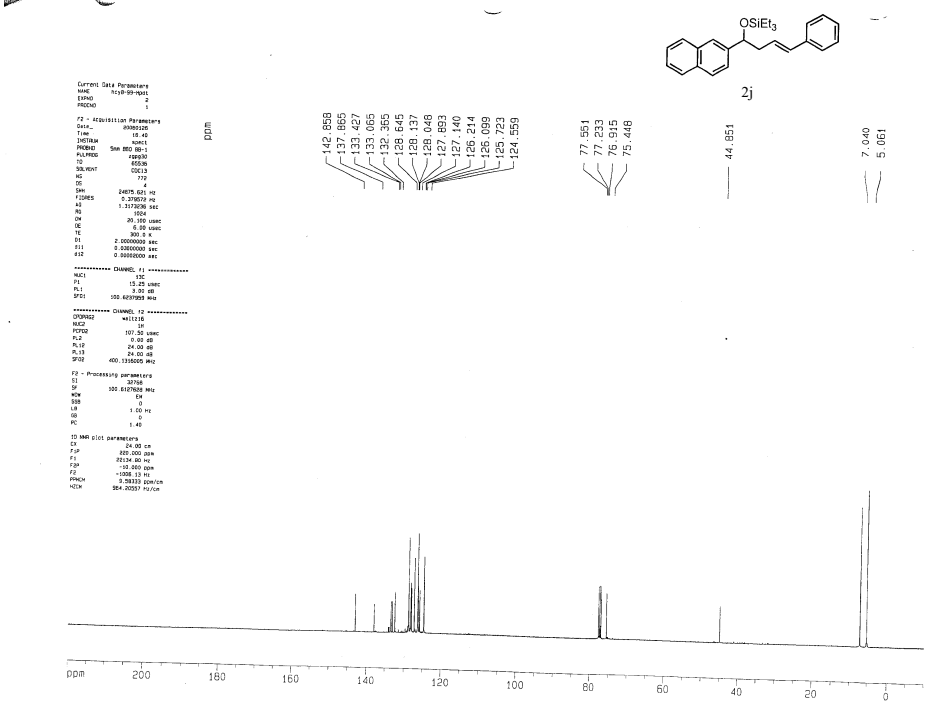
S 43


OSiEt3
Ph
MeO
2i-para
ppm
158.967
138.050
137.655
132.265
128.741
127.466
127.287
127.203
126.295
113.694
77.699
77.381
77.064
75.043
55.366
45.069
7.130
5.165
ppm 200 180 160 140 120 100 80 60 40 20 0

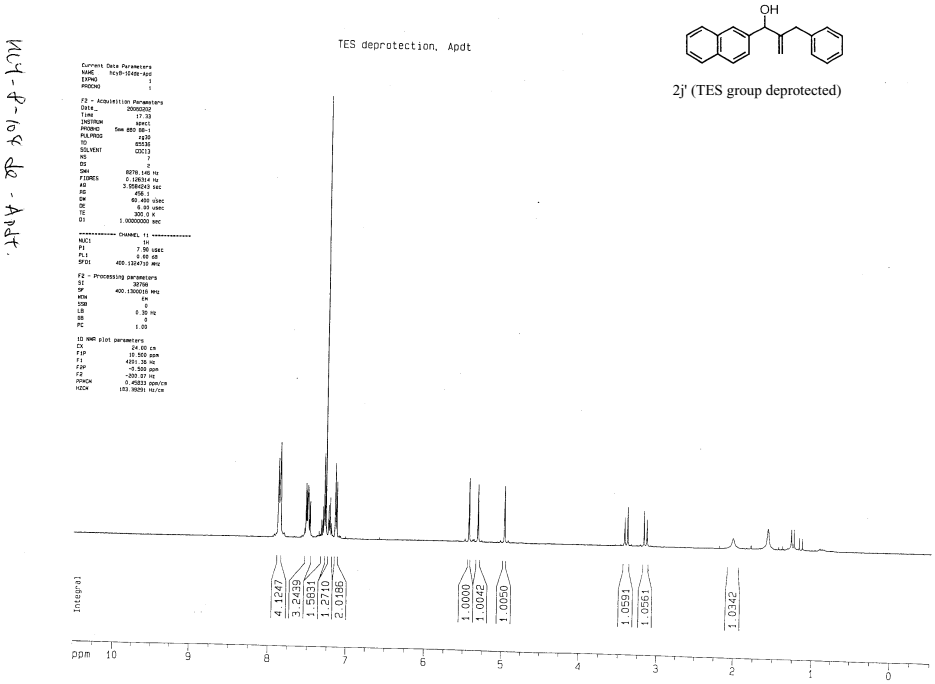
S 44


H-pdt
OSiEt3
2j
Integral
3.2359
1.1140
1.0446
1.9690
5.1339
1.5549
1.0448
1.0898
1.0000
2.1599
9.7690
6.2220
ppm 10 9 8 7 6 5 4 3 2 1 0

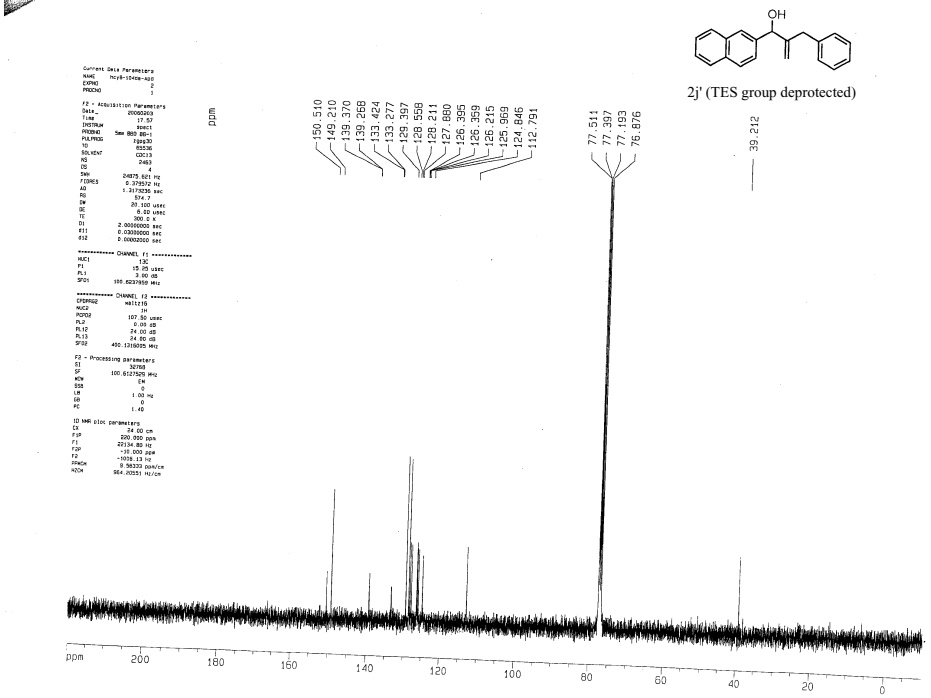
S 45


OSiEt3
2j
ppm
142.858
137.865
133.427
133.065
132.365
128.645
128.137
128.048
127.883
127.140
126.214
126.099
125.723
124.559
77.551
77.233
76.915
75.448
44.851
7.040
5.061
ppm 200 180 160 140 120 100 80 60 40 20 0

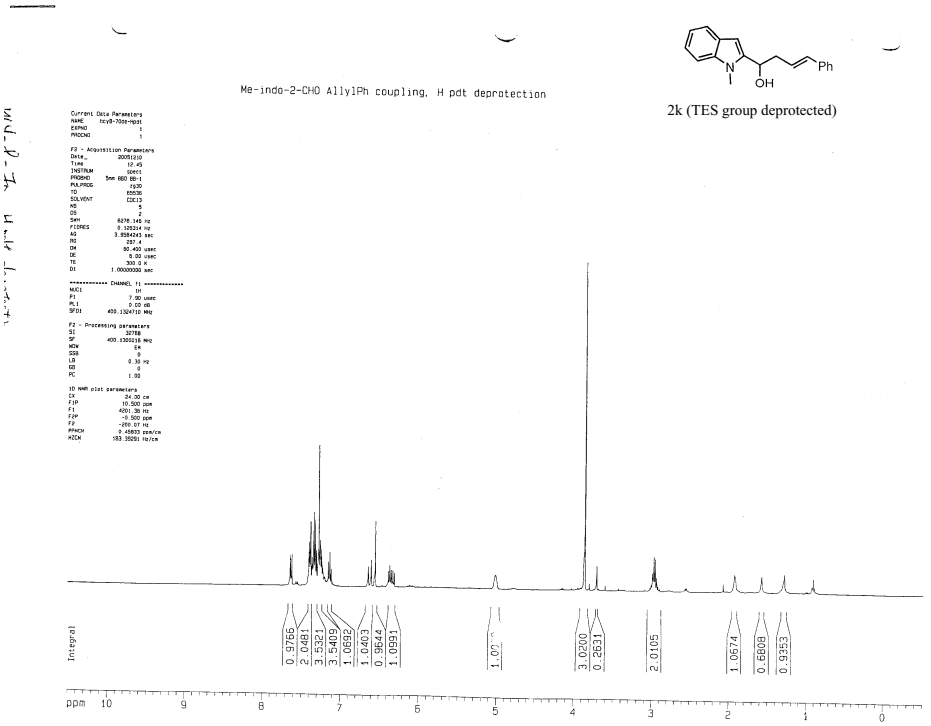
S 46


TES deprotection, Apdt
OH
2j' (TES group deprotected)
Integral
4.1247
3.2439
1.5831
1.2710
2.0186
1.0000
1.0042
1.0050
1.0591
1.0561
1.0342
ppm 10 9 8 7 6 5 4 3 2 1 0

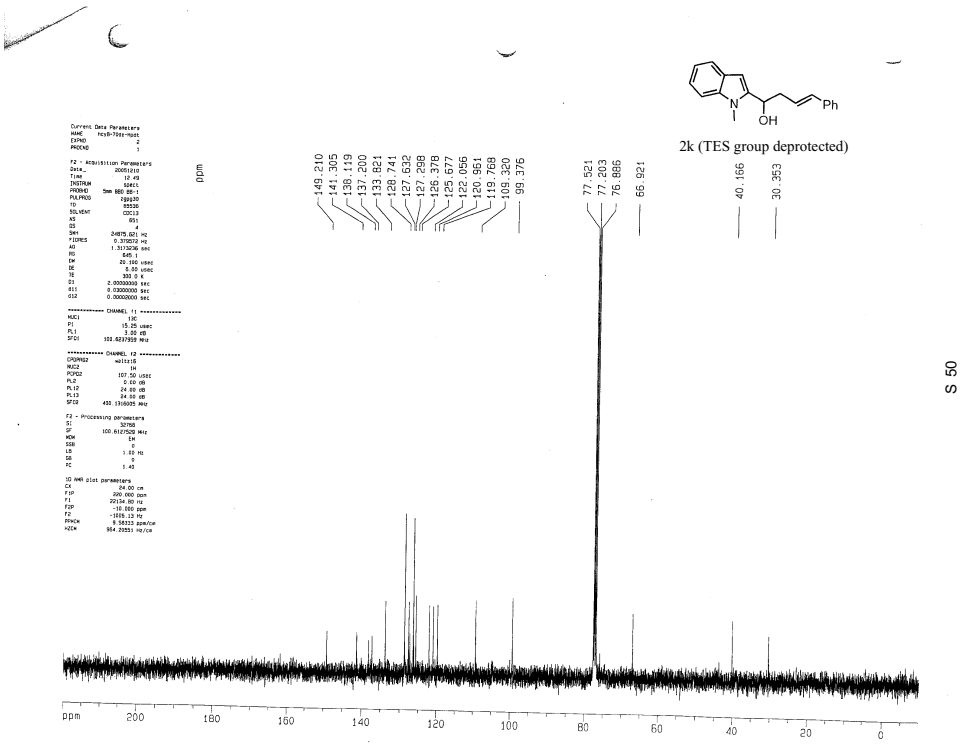
S 47


OH
2j' (TES group deprotected)
150.510
149.210
139.370
139.258
133.424
133.277
129.397
128.558
128.211
127.880
126.395
126.359
126.215
125.969
124.846
112.791
77.511
77.397
77.193
76.876
39.212
ppm
200
180
160
140
120
100
80
60
40
20
0

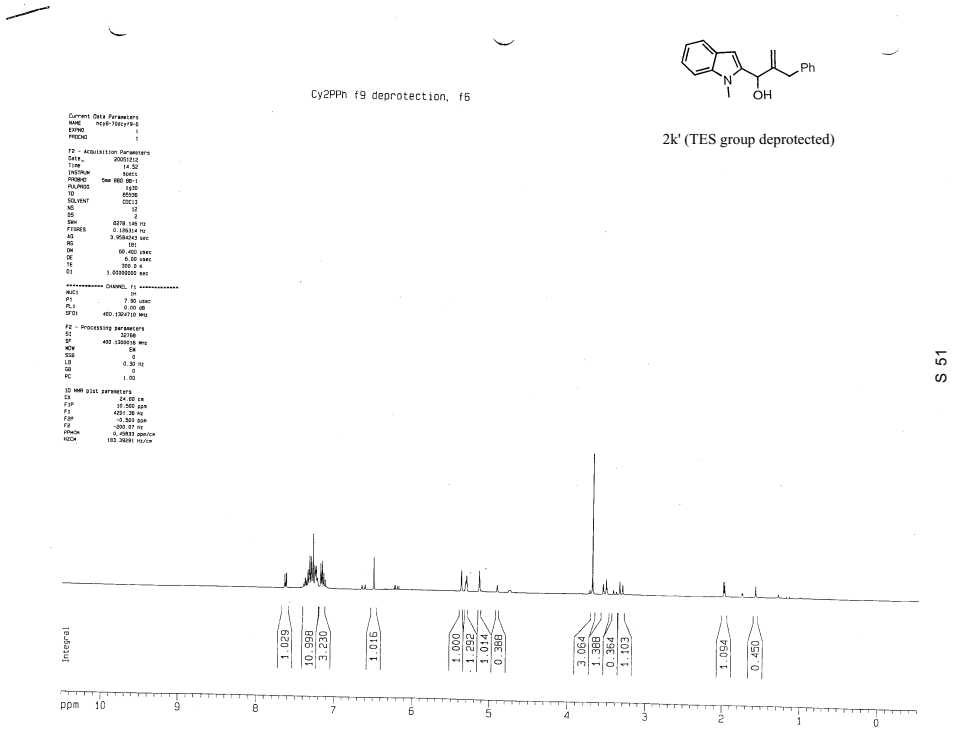
S 48


Me-indo-2-CHO AllylPh coupling, H pdt deprotection
N
OH
Ph
2k (TES group deprotected)
Integral
0.9756
2.0481
3.5321
3.5409
1.0692
1.0403
0.9644
1.0991
1.00
3.0200
0.2631
2.0105
1.0674
0.6608
0.9353
ppm
10
9
8
7
6
5
4
3
2
1
0

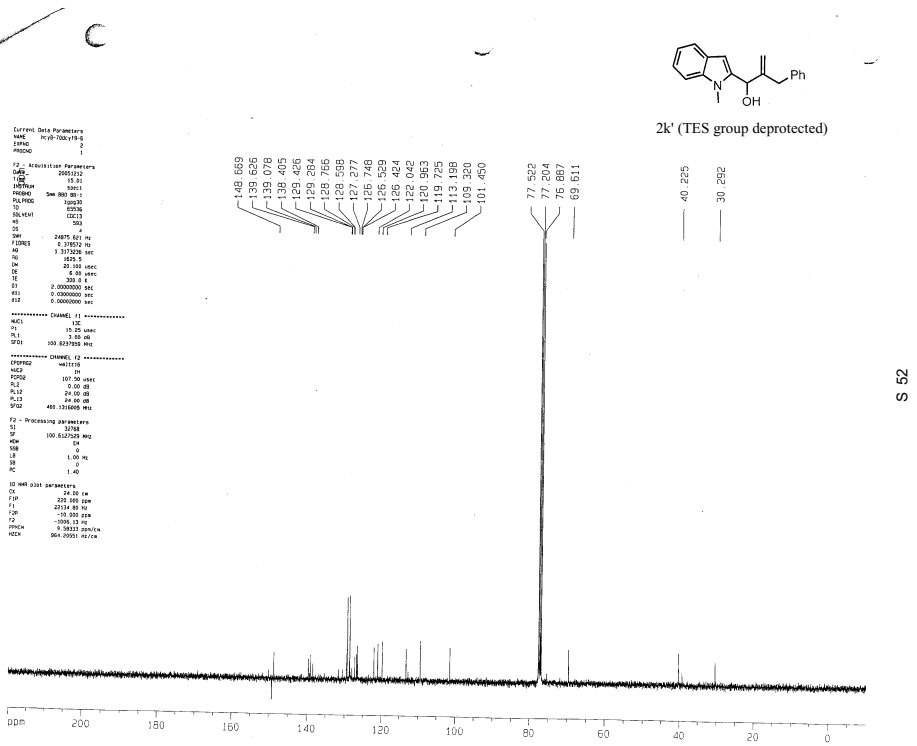
S 49


2k (TES group deprotected)
149.210
141.305
138.119
137.200
133.821
128.741
127.632
127.298
126.378
125.677
122.056
120.961
119.768
109.320
99.376
77.521
77.203
76.886
66.921
40.166
30.353
ppm

S 50

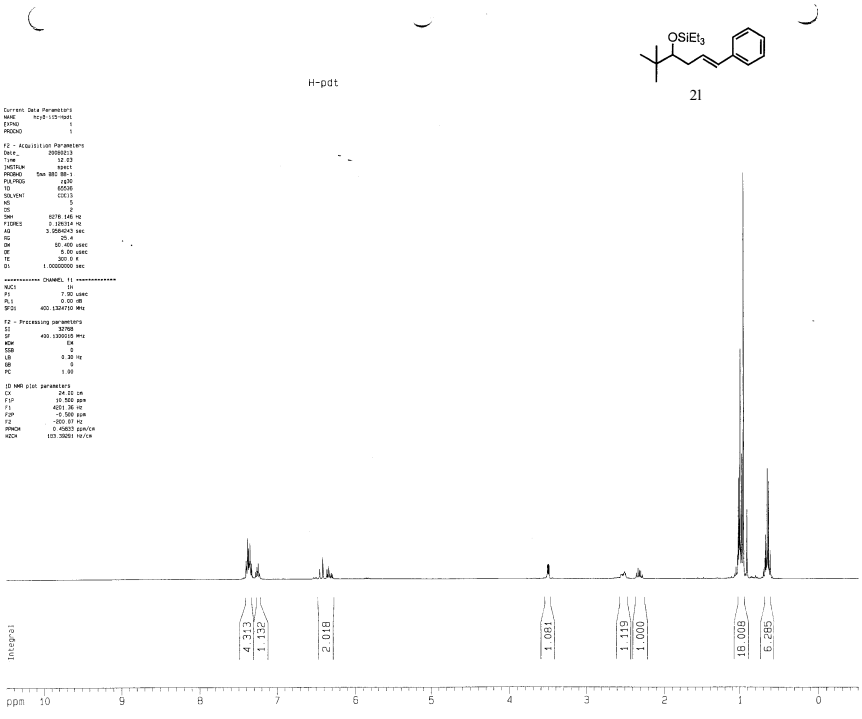

Cy2PPh f9 deprotection, f6
2k' (TES group deprotected)
Integral
1.029
10.998
3.230
1.016
1.000
1.292
1.014
0.388
3.064
1.388
0.364
1.103
1.094
0.450
ppm

S 51

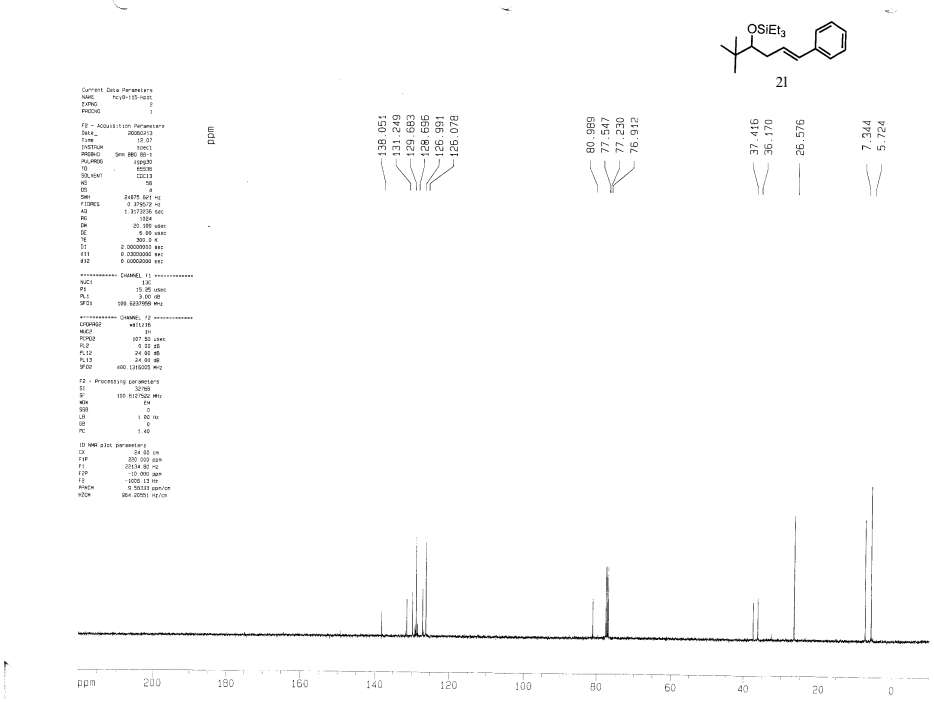


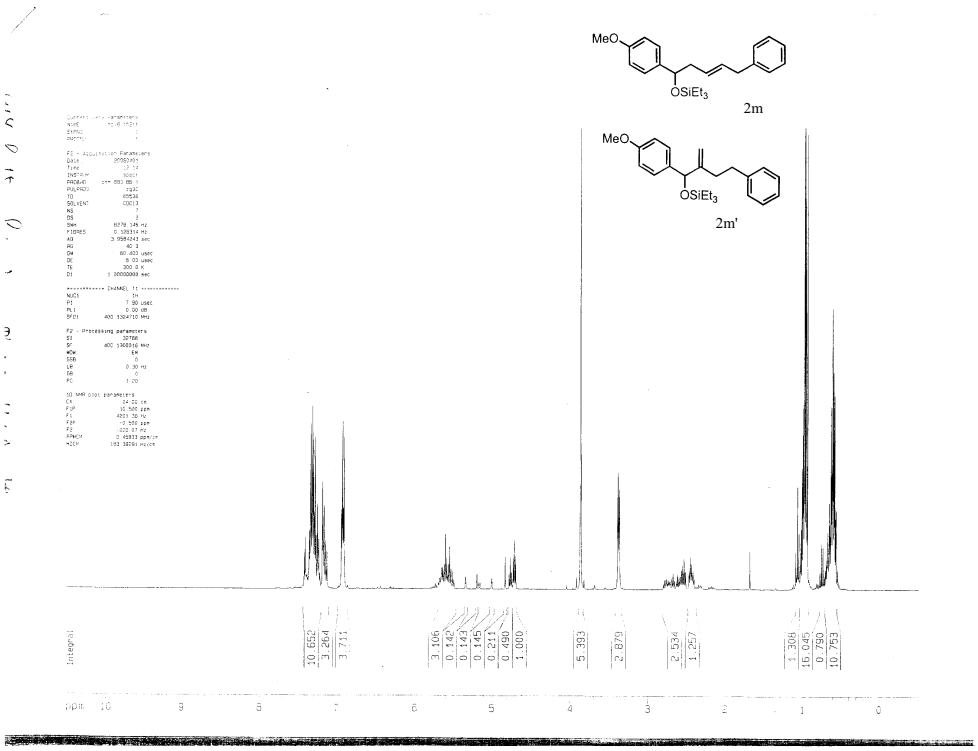
2k' (TES group deprotected)

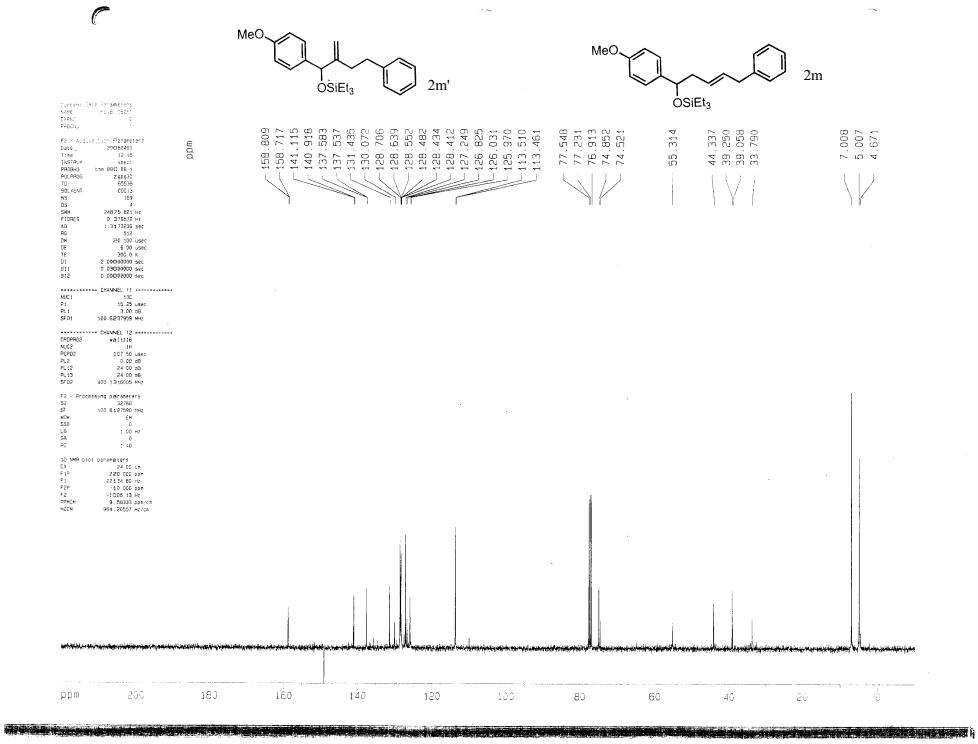
S 52

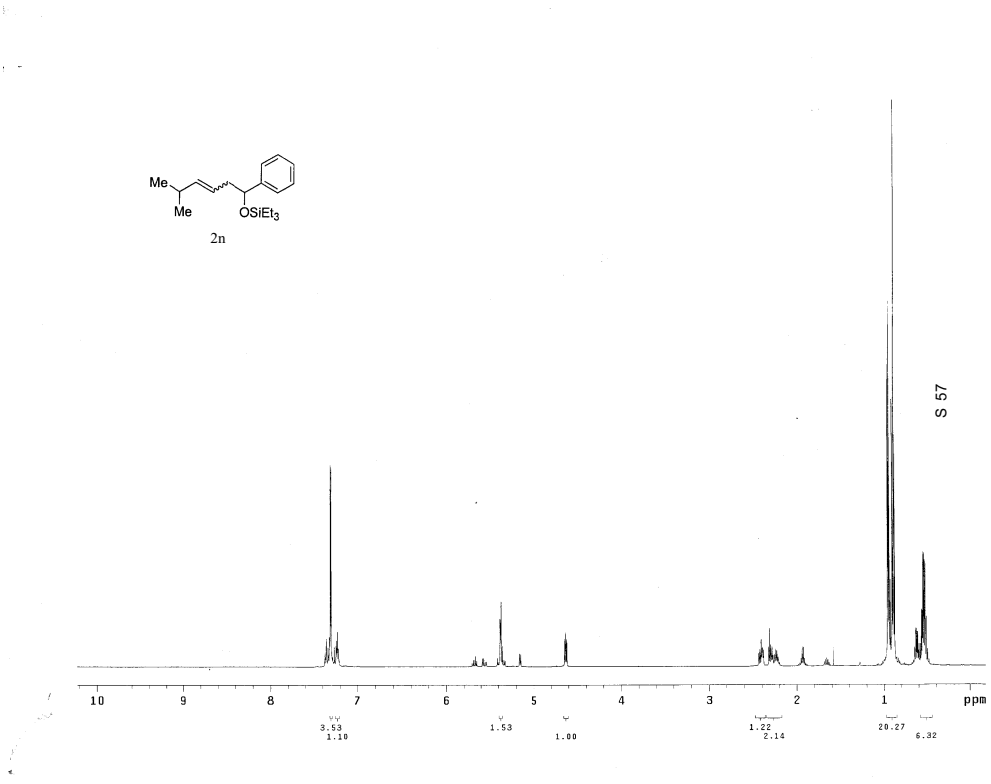


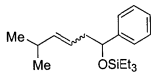
21


OSiEt3
21
138.051
131.249
129.683
128.696
126.991
126.078
80.989
77.547
77.230
76.912
37.416
36.170
26.576
7.344
5.724
ppm

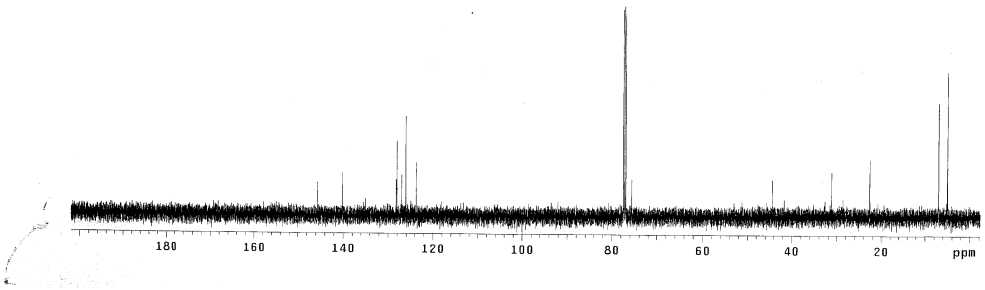

MeO
OSiEt3
2m
MeO
OSiEt3
2m'
10.652
3.264
3.711
3.106
0.142
0.145
0.211
0.490
1.000
5.393
2.879
2.534
1.257
1.306
16.045
0.790
10.753
ppm

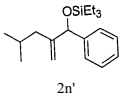

MeO
OSiEt3
2m'
MeO
OSiEt3
2m
ppm
159.809
158.717
141.115
140.916
137.583
137.537
131.435
130.072
128.706
128.639
128.552
128.482
128.434
128.412
127.249
126.825
126.031
125.970
113.510
113.461
77.548
77.231
76.913
74.882
74.521
55.314
44.337
39.250
39.058
33.790
7.008
5.007
4.671
ppm
200
180
160
140
120
100
80
60
40
20
0


Me
Me
OSiEt3
2n
S 57
10
9
8
7
6
5
4
3
2
1
ppm
3.53
1.10
1.53
1.00
1.22
2.14
20.27
6.32



2n





2n'

SN050726 allylic alcohol


```
Current Data Parameters
NAME          SN726-all-H
EXPNO                   1
PROCNO                  1

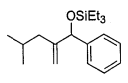
F2 - Acquisition Parameters
Date_           20050722
Time              21.51
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG           zg30
TD               65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                   32
DW               60.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec

============ CHANNEL f1 =========
NUC1                 1H
P1                7.90 usec
PL1               0.00 dB
SFO1        400.1324710 MHz

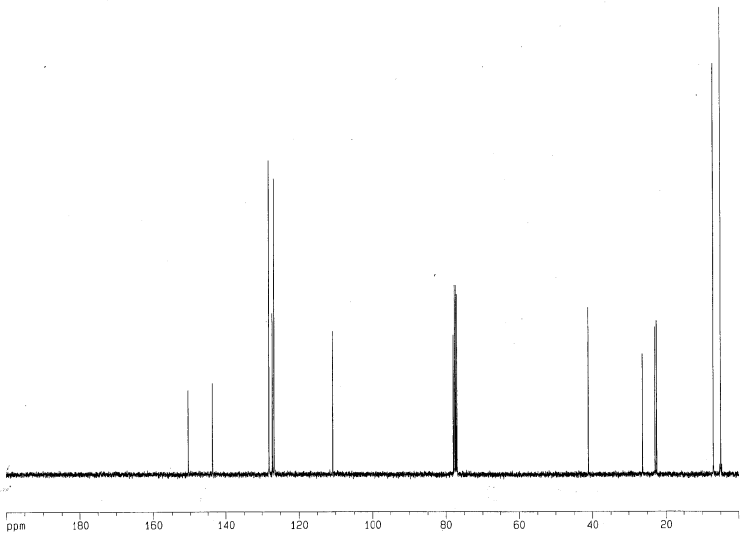
F2 - Processing parameters
SI                32768
SF          400.1300056 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                1.00

1D NMR plot parameters
CX               20.00 cm
F1P              10.000 ppm
F1             4001.30 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM         0.50000 ppm/cm
HZCM        200.06500 Hz/cm
```

SN050726 allylic alcohol



2n'




```
Current Data Parameters
NAME          SN726-all-C
EXPNO                   1
PROCNO                  1

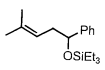
F2 - Acquisition Parameters
Date_          20050722
Time              21.53
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  159
DS                    4
SWH           25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG                 8192
DW               19.900 usec
DE                6.00 usec
TE                300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

============ CHANNEL f1 ============
NUC1                13C
P1                15.25 usec
PL1               3.00 dB
SFO1         100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2          waltz16
NUC2                1H
PCPD2            107.50 usec
PL2               0.00 dB
PL12              24.00 dB
PL13              24.00 dB
SFO2         400.1318005 MHz

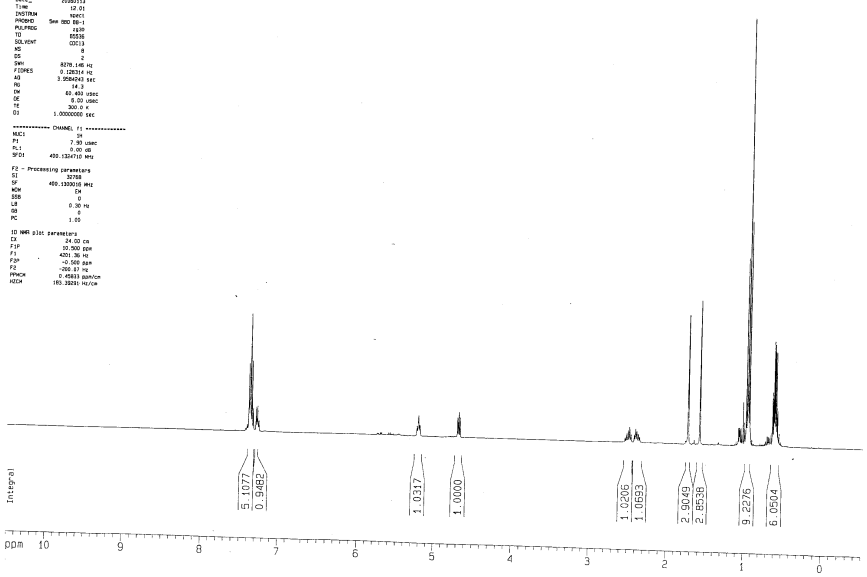
F2 - Processing parameters
SI                 32768
SF           100.6127499 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                  1.40

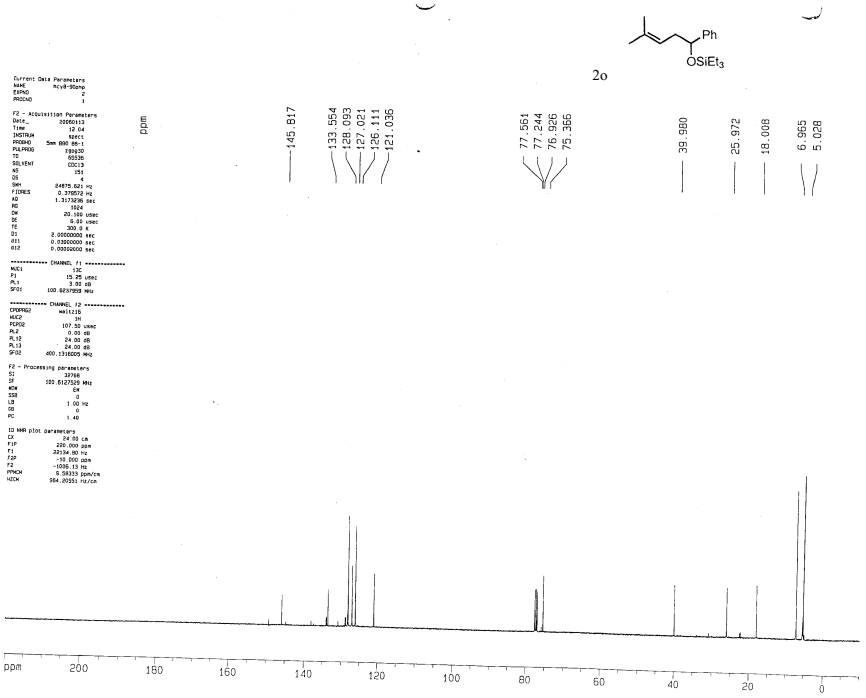
1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P               0.000 ppm
F2                0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM          1006.12744 Hz/cm
```



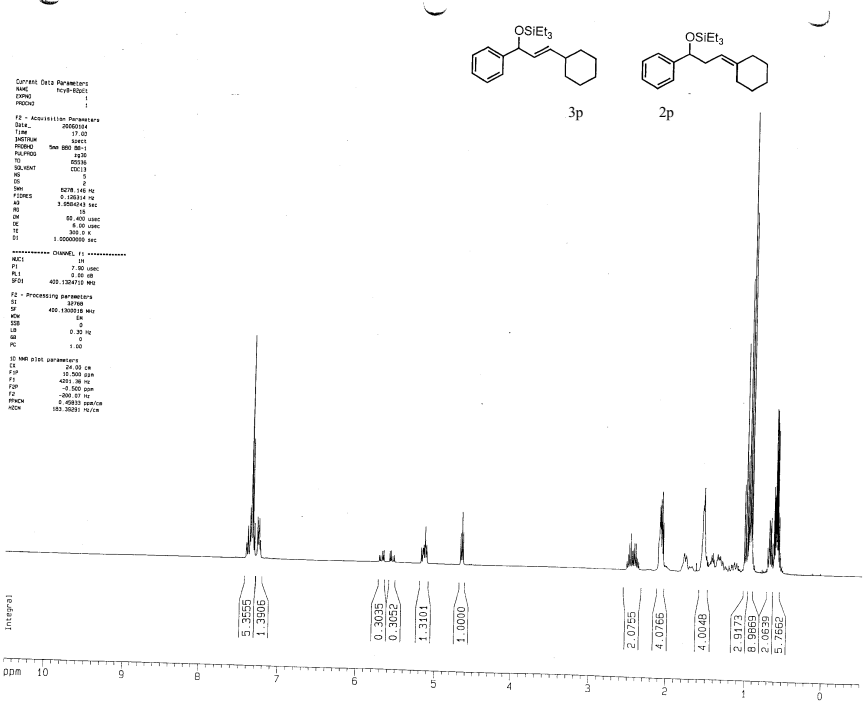
2o

S 61

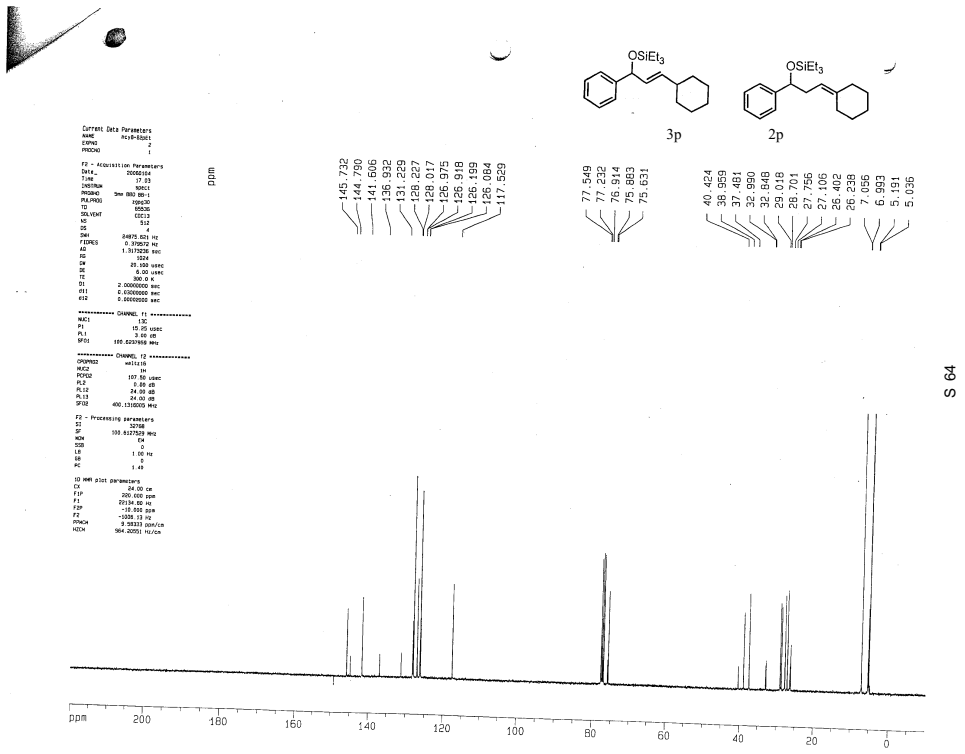



Ph
OSiEt3
2o
ppm
145.817
133.554
128.093
127.021
126.111
121.036
77.561
77.244
76.926
75.366
39.980
25.972
18.008
6.965
5.028
ppm 200 180 160 140 120 100 80 60 40 20 0

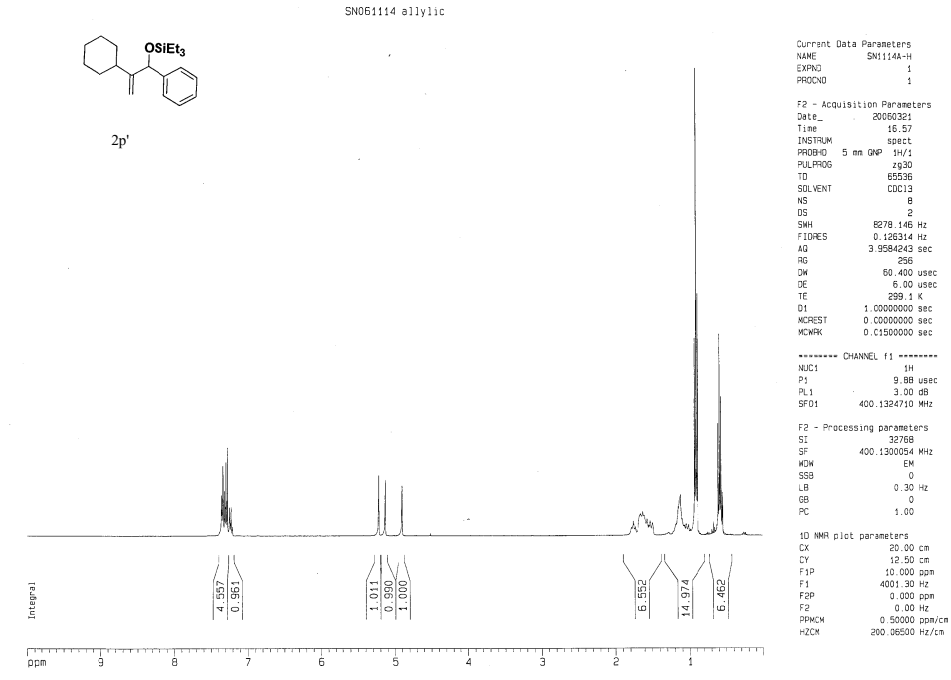
S 62

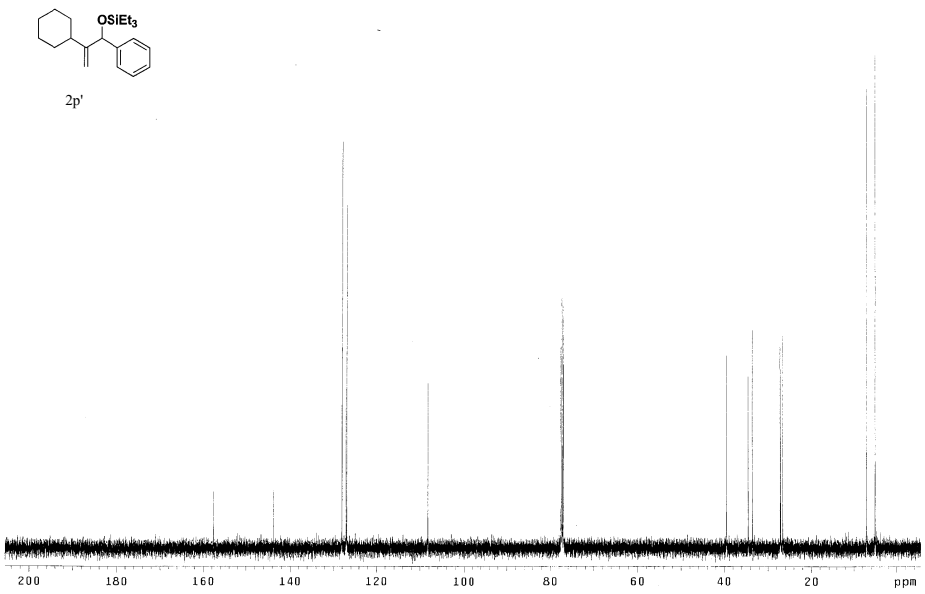

OSiEt3
3p
OSiEt3
2p
Integral
5.3555
1.3906
0.3035
0.3052
1.3101
1.0000
2.0755
4.0766
4.0048
2.9173
8.9869
2.0639
5.7662
ppm 10 9 8 7 6 5 4 3 2 1 0

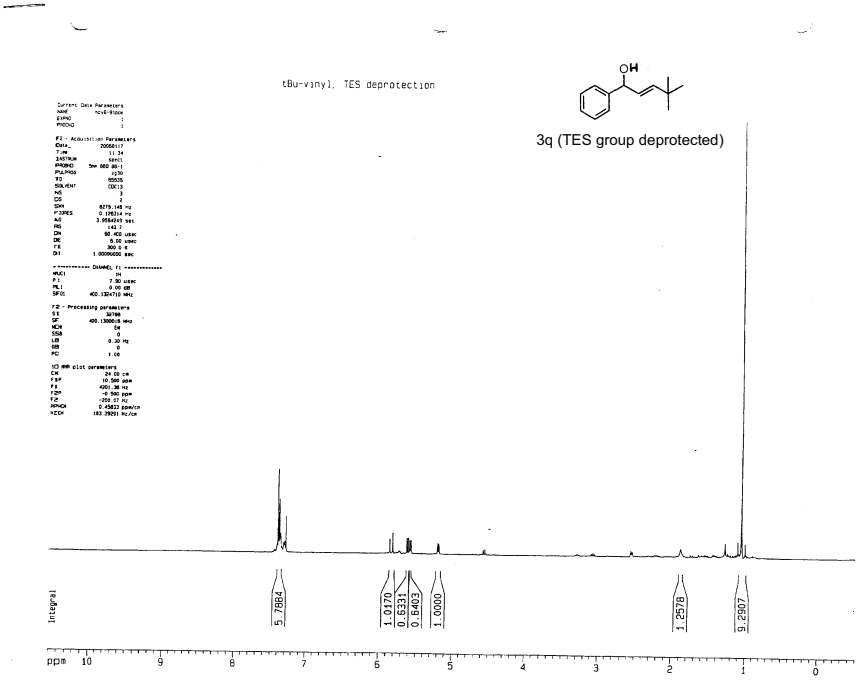
S 63

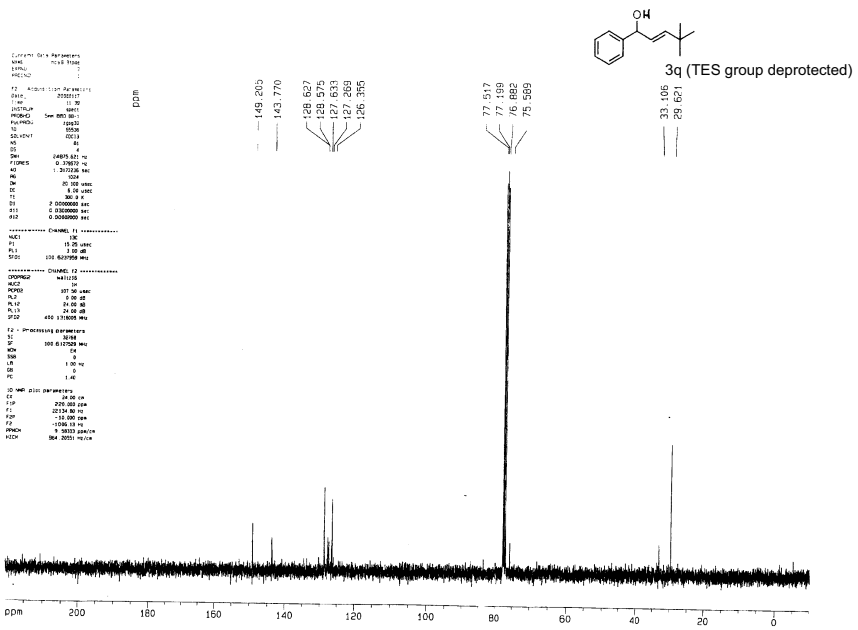

OSiEt3
3p
OSiEt3
2p
Current Data Parameters
NAME Acid-Basic
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060104
Time 17.03
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 24975.021 Hz
FIDRES 0.379572 Hz
AQ 1.3173236 sec
RG 1024
DW 20.100 usec
DE 6.00 usec
TE 600.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00020000 sec
********** CHANNEL f1 **********
NUC1 13C
P1 15.25 usec
PL1 3.00 dB
SFO1 100.6237858 MHz
********** CHANNEL f2 **********
CPDPRG2 waltz16
NUC2 1H
PCPD2 107.50 usec
PL2 0.00 dB
PL12 24.00 dB
PL13 24.00 dB
SFO2 400.1310005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127529 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 24.00 cm
F1P 200.000 ppm
F1 20134.60 Hz
F2P -10.000 ppm
F2 -1006.13 Hz
PPMCM 9.16333 ppm/cm
HZCM 964.20551 Hz/cm
ppm
145.732
144.790
141.606
136.932
131.229
128.227
128.017
126.975
126.918
126.199
126.084
117.529
77.549
77.232
76.914
75.863
75.631
40.424
38.959
37.481
32.990
32.848
29.018
28.701
27.756
27.106
26.402
26.238
7.056
6.993
5.191
5.036
ppm
200
180
160
140
120
100
80
60
40
20
0

S 64

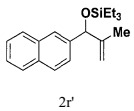

SN061114 allylic
OSiEt3
2p'
Integral
4.557
0.961
1.011
0.990
1.000
6.552
14.974
6.462
ppm
9
8
7
6
5
4
3
2
1
Current Data Parameters
NAME SN1114A-H
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060321
Time 16.57
INSTRUM spect
PROBHD 5 mm GNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 256
DW 60.400 usec
DE 6.00 usec
TE 299.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm


OSiEt3
2p'
200
180
160
140
120
100
80
60
40
20
ppm


tBu-vinyl, TES deprotection
OH
3q (TES group deprotected)
5.7884
1.0170
0.6331
0.6403
1.0000
1.2578
9.2907
Integral
ppm



SN050835 allylic



2r'

Current Data Parameters
NAME SN835-all-H
EXPNO 1
PROCNO 1

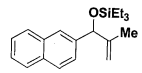
F2 - Acquisition Parameters
Date_ 20051014
Time 12.08
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 71.8
DW 60.400 usec
DE 6.00 usec
TE 294.8 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 9.88 usec
PL1 3.00 dB
SFO1 400.1324710 MHz

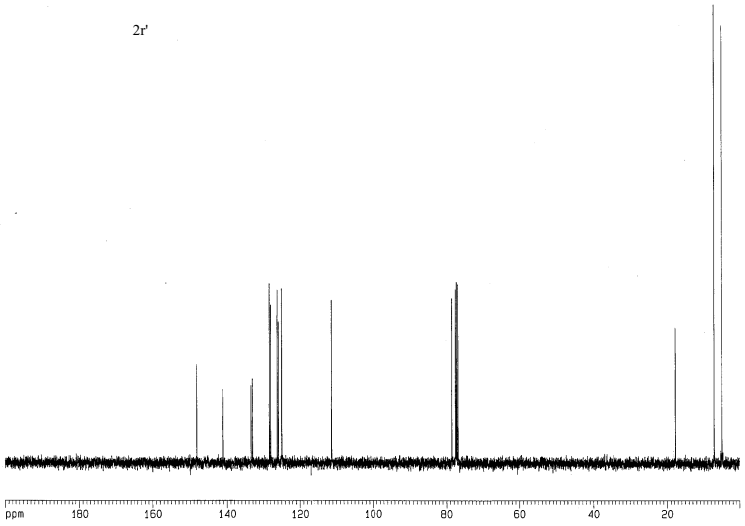
F2 - Processing parameters
SI 32768
SF 400.1300059 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 12.50 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm

SN050835 allylic



2r'




```
Current Data Parameters
NAME        SN035-all-C
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20051014
Time              12.16
INSTRUM           spect
PROBHD  5 mm QNP  1H/1
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 193
DS                   4
SWH          23980.814 Hz
FIDRES        0.365918 Hz
AQ            1.3654756 sec
RG               2896.3
DW              20.850 usec
DE               6.00 usec
TE              294.8 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

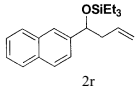
======== CHANNEL f1 ========
NUC1                 13C
P1                 8.50 usec
PL1                3.00 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             88.01 usec
PL2                3.00 dB
PL12              22.00 dB
PL13              22.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF          100.6127535 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                 20.00 cm
CY                 12.50 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          10.00000 ppm/cm
HZCM         1006.12756 Hz/cm
```

SN050835 homoallylic



2r


```
Current Data Parameters
NAME          SN035-ho-C
EXPNO                 1
PROCNO                1

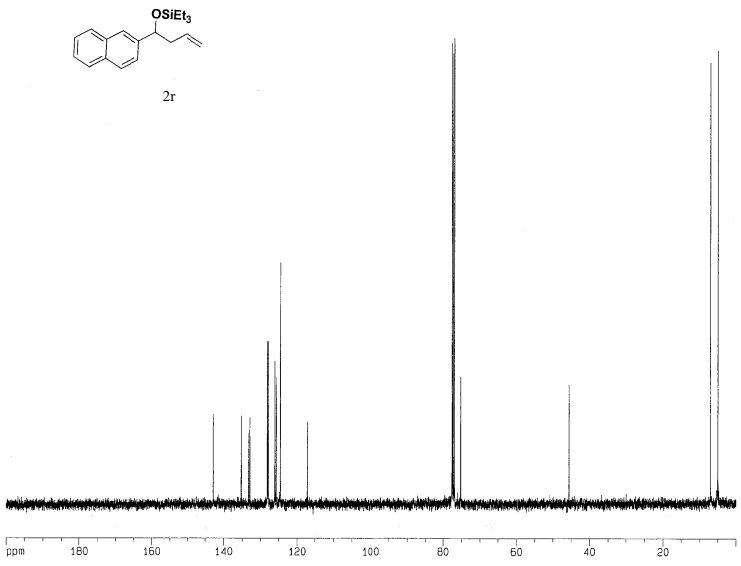
F2 - Acquisition Parameters
Date_          20051014
Time              12.27
INSTRUM           spect
PROBHD  5 mm QNP  1H/1
PULPROG             zg30
TD               65536
SOLVENT          CDCl3
NS                   8
DS                   2
SWH          8278.146 Hz
FIDRES       0.126314 Hz
AQ            3.9584243 sec
RG                1283.7
DW              60.400 usec
DE               6.00 usec
TE              294.8 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.88 usec
PL1                3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                  32768
SF          400.1300054 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                 20.00 cm
CY                 12.50 cm
F1P              10.000 ppm
F1             4001.30 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM          0.50000 ppm/cm
HZCM         200.06500 Hz/cm
```

SN050835 homoallylic



2r

```
Current Data Parameters
NAME            SN835-ho-C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_          20051015
Time              12.12
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 302
DS                   4
SWH          25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG                2048
DW              19.900 usec
DE               6.00 usec
TE              300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

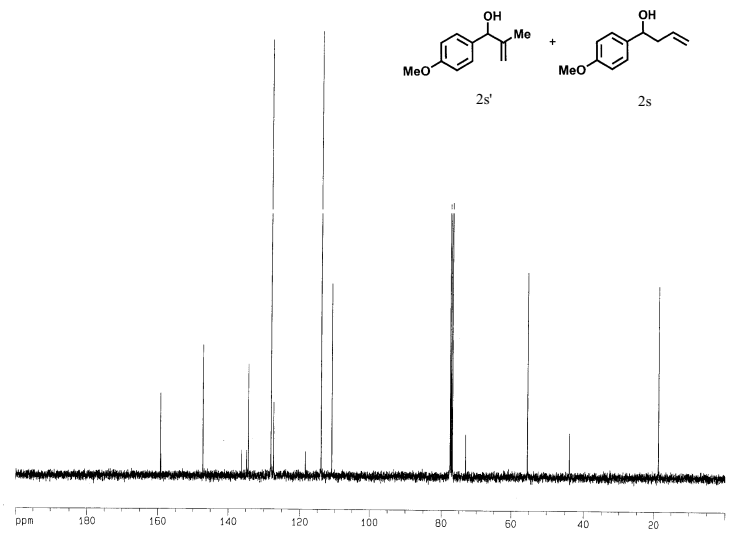
============ CHANNEL f1 ============
NUC1               13C
P1               15.25 usec
PL1               3.00 dB
SFO1       100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2         waltz16
NUC2               1H
PCPD2          107.50 usec
PL2               0.00 dB
PL12             24.00 dB
PL13             24.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127507 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P              0.000 ppm
F2               0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM       1006.12738 Hz/cm
```

SN061027 TBAF



2s' 2s

```
Current Data Parameters
NAME          SN1027-TBAF-C
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_          20061031
Time              19.23
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                  98
DS                   4
SWH          25125.629 Hz
FIDRES        0.383387 Hz
AQ            1.3042164 sec
RG               3649.1
DW              19.900 usec
DE               6.00 usec
TE              300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

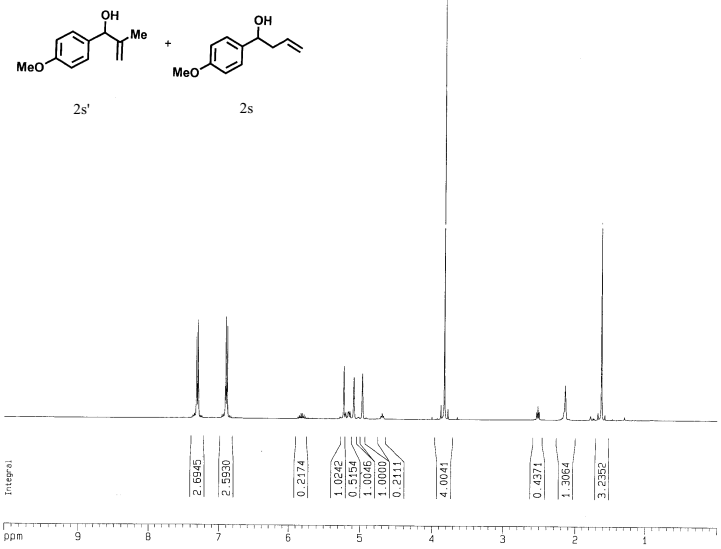
============ CHANNEL f1 ============
NUC1               13C
P1               15.25 usec
PL1               3.00 dB
SFO1       100.6237959 MHz

============ CHANNEL f2 ============
CPDPRG2         waltz16
NUC2               1H
PCPD2          107.50 usec
PL2               0.00 dB
PL12             24.00 dB
PL13             24.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127553 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P              200.000 ppm
F1             20122.55 Hz
F2P              0.000 ppm
F2               0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM       1006.12756 Hz/cm
```

SN061027 TBAF



Current Data Parameters
NAME SN1027-TBAF-H
EXPNO 1
PROCNO 1

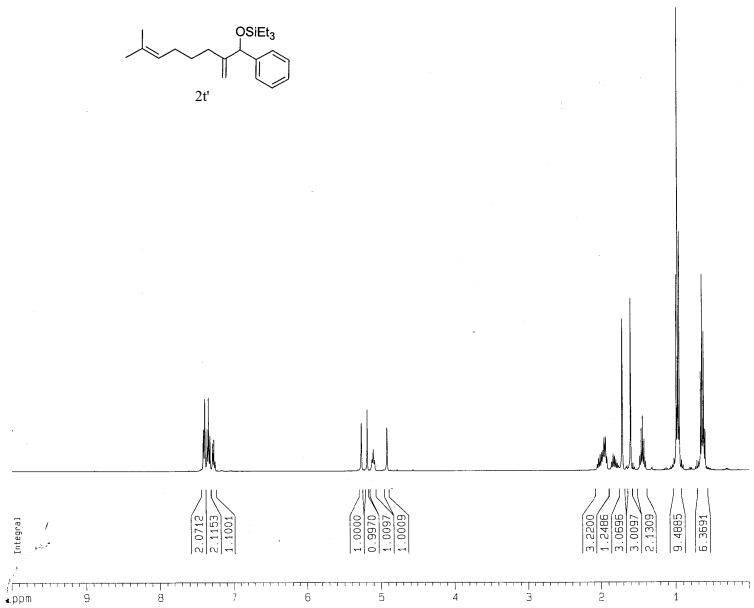
F2 - Acquisition Parameters
Date_ 20060131
Time 19.16
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 57
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm

SN050672 a



Current Data Parameters
NAME SN672-a-H
EXPNO 1
PROCNO 1

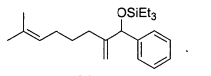
F2 - Acquisition Parameters
Date_ 20050625
Time 16.55
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 32
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 9.50 usec
PL1 2.00 dB
SFO1 400.1324710 MHz

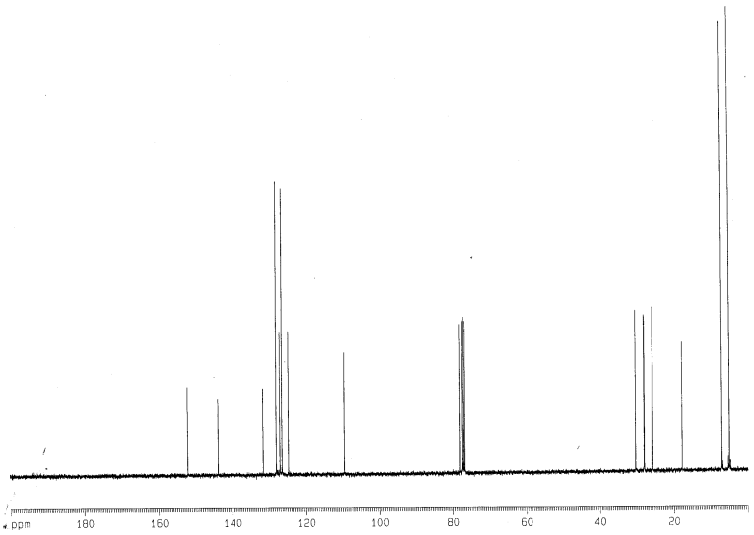
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 4001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06500 Hz/cm

SN050672 a



2t'




```
Current Data Parameters
NAME          SN672-a-C
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_        20050625
Time              18.00
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 760
DS                   4
SWH          24330.900 Hz
FIDRES        0.371260 Hz
AQ            1.3468148 sec
RG               1824.6
DW              20.550 usec
DE               6.00 usec
TE              300.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

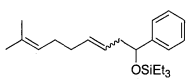
============ CHANNEL f1 =============
NUC1               13C
P1                8.50 usec
PL1               3.00 dB
SFO1       100.6237959 MHz

============ CHANNEL f2 =============
CPDPRG2         waltz16
NUC2                1H
PCPD2          100.00 usec
PL2              2.00 dB
PL12            22.00 dB
PL13            22.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127518 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX               20.00 cm
F1P             200.000 ppm
F1            20122.55 Hz
F2P             0.000 ppm
F2              0.00 Hz
PPMCM         10.00000 ppm/cm
HZCM       1006.12756 Hz/cm
```

SN050672-b



2t

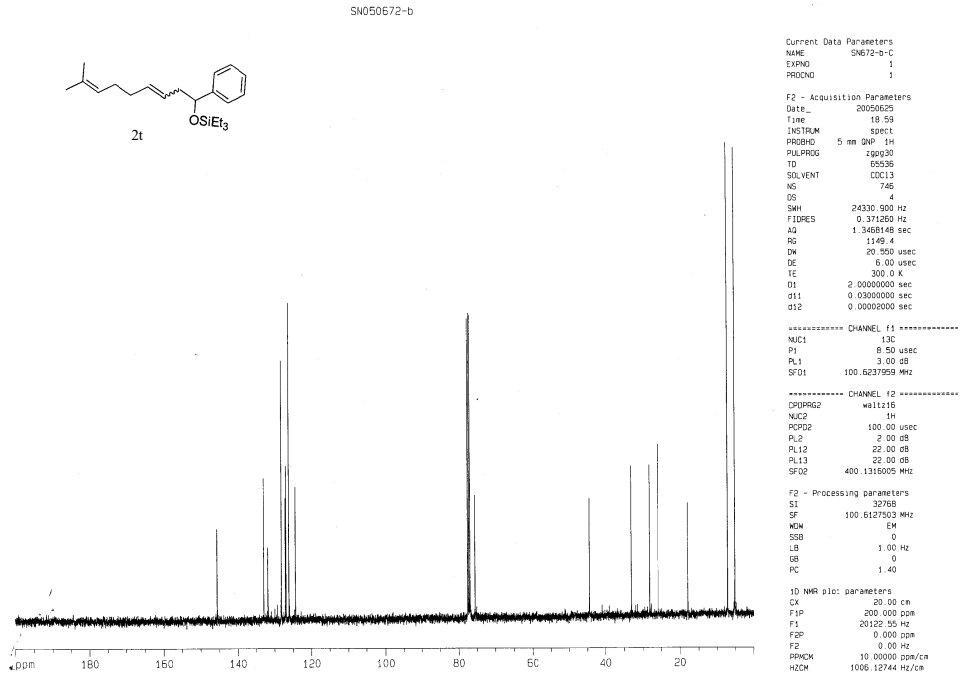

```
Current Data Parameters
NAME          SN672-b-H
EXPNO                1
PROCNO               1

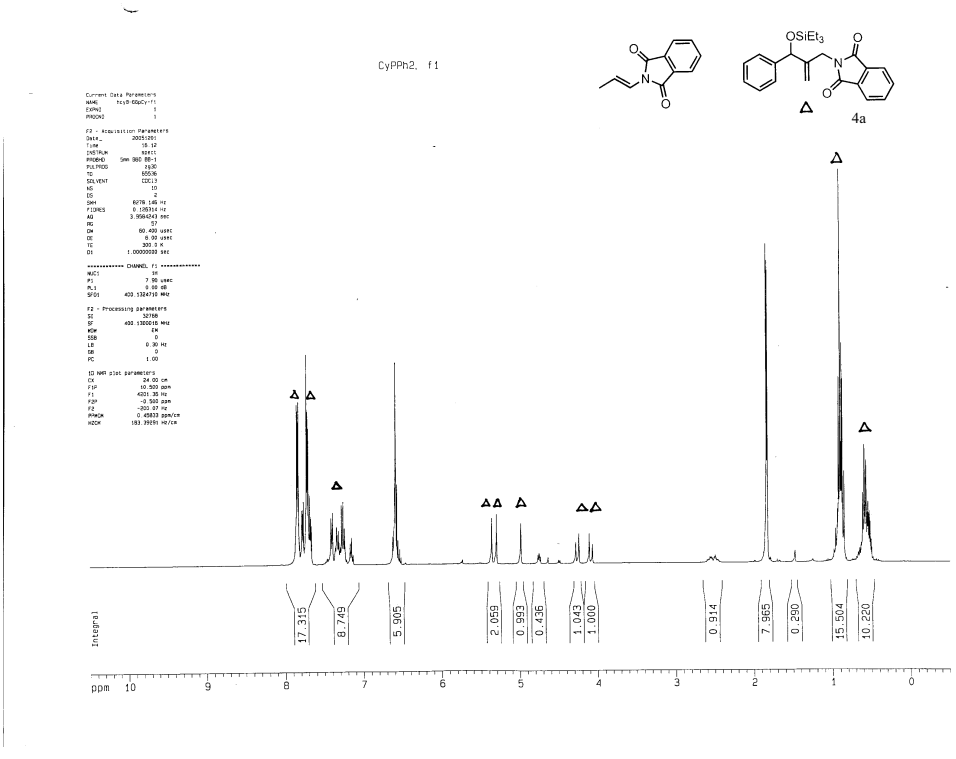
F2 - Acquisition Parameters
Date_        20050625
Time              18.50
INSTRUM           spect
PROBHD     5 mm QNP  1H
PULPROG             zg30
TD               65536
SOLVENT          CDCl3
NS                   8
DS                   4
SWH          8278.146 Hz
FIDRES       0.126314 Hz
AQ            3.9584243 sec
RG                  54
DW              60.400 usec
DE               6.00 usec
TE              300.0 K
D1           1.00000000 sec

============ CHANNEL f1 =============
NUC1                1H
P1                9.50 usec
PL1               2.00 dB
SFO1       400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1300000 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX               20.00 cm
F1P              10.000 ppm
F1            4001.30 Hz
F2P              0.000 ppm
F2               0.00 Hz
PPMCM         0.50000 ppm/cm
HZCM       200.06500 Hz/cm
```


SN050672-b
OSiEt3
2t
Current Data Parameters
NAME SN672-b-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050625
Time 18.59
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 746
DS 4
SWH 24330.900 Hz
FIDRES 0.371260 Hz
AQ 1.3468148 sec
RG 1149.4
DW 20.550 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 8.50 usec
PL1 3.00 dB
SFO1 100.6237959 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 2.00 dB
PL12 22.00 dB
PL13 22.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127503 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 200.000 ppm
F1 20122.55 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 10.00000 ppm/cm
HZCM 1006.12744 Hz/cm
ppm 180 160 140 120 100 80 60 40 20


CyPPh2, f1
OSiEt3
4a
Integral
17.315
8.749
5.905
2.059
0.993
0.436
1.043
1.000
0.914
7.965
0.290
15.504
10.220
ppm 10 9 8 7 6 5 4 3 2 1 0

4a'

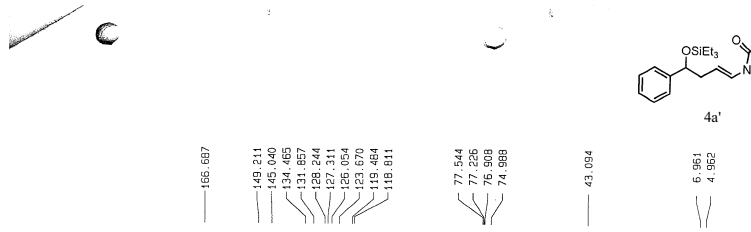

```
Current Data Parameters
NAME          hcy-B-51-pf1
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_          20051108
Time               16.12
INSTRUM            spect
PROBHD     5mm BBO BB-1
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    6
DS                    2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                 71.8
DW               60.400 usec
DE                6.00 usec
TE               300.0 K
D1            1.00000000 sec

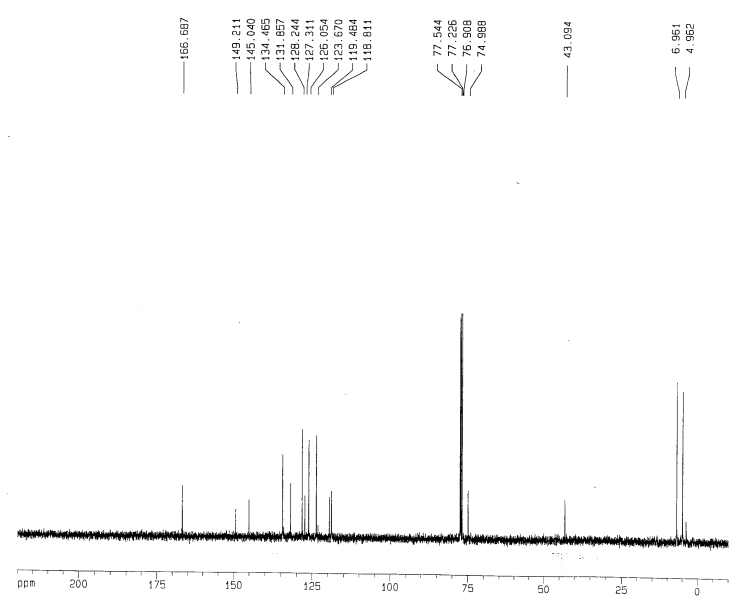
========== CHANNEL f1 ==========
NUC1                 1H
P1                7.90 usec
PL1               0.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1300016 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                20.00 cm
F1P               10.500 ppm
F1              4201.37 Hz
F2P               -0.500 ppm
F2              -200.07 Hz
PPMCM             0.55000 ppm/cm
HZCM            220.07150 Hz/cm
```



4a'




```
Current Data Parameters
NAME          hcy-B-51-pf1
EXPNO                    2
PROCNO                   1

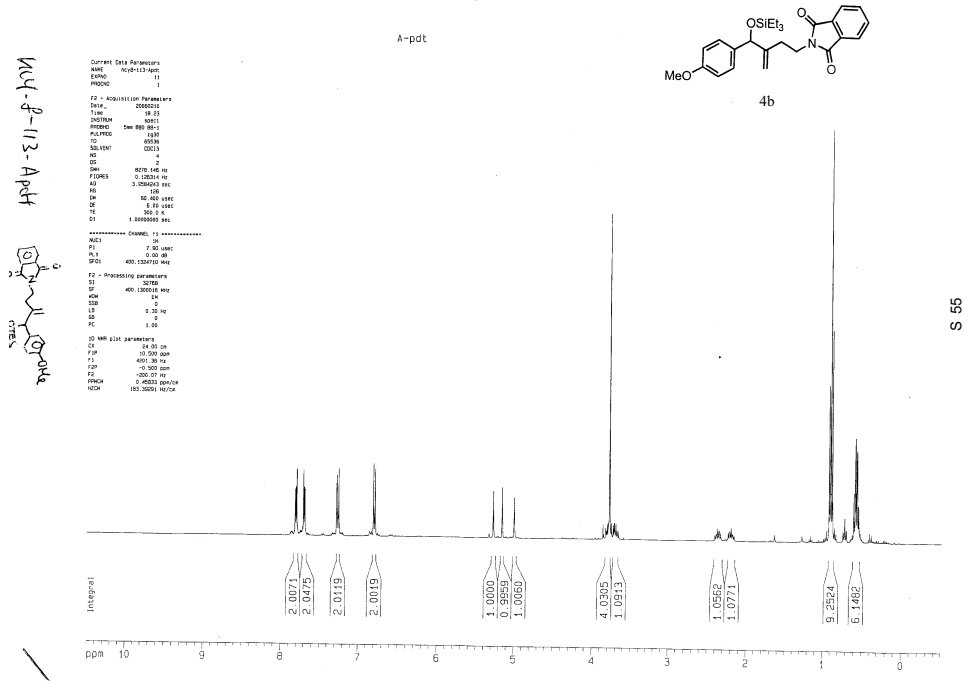
F2 - Acquisition Parameters
Date_          20051108
Time               16.19
INSTRUM            spect
PROBHD     5mm BBO BB-1
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  103
DS                    4
SWH          24875.621 Hz
FIDRES        0.379572 Hz
AQ            1.3173236 sec
RG                 1024
DW               20.100 usec
DE                6.00 usec
TE               300.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

========== CHANNEL f1 ==========
NUC1                 13C
P1               15.25 usec
PL1               3.00 dB
SFO1        100.6237959 MHz

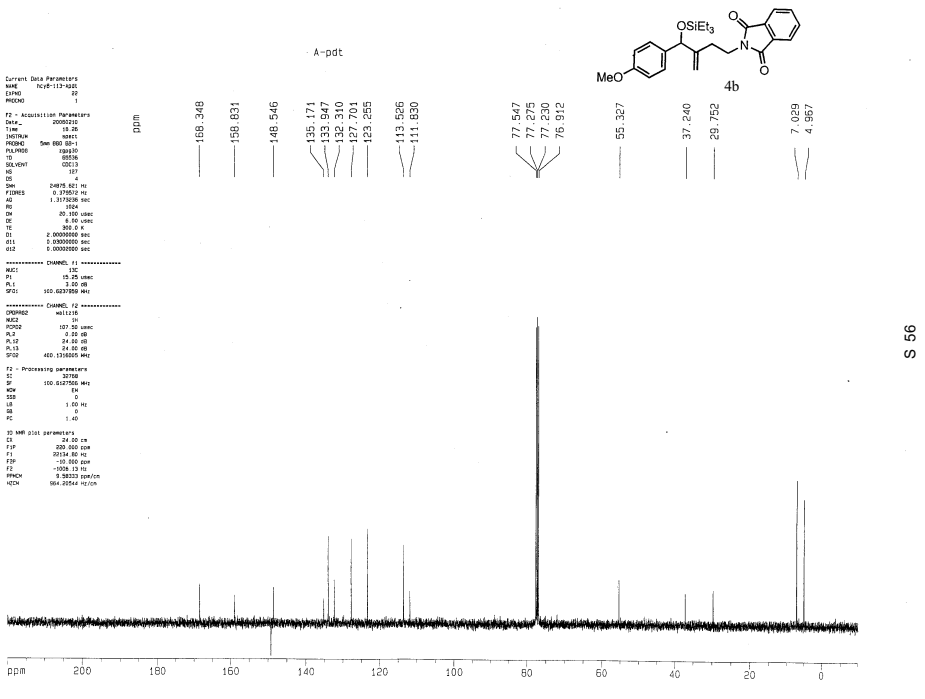
========== CHANNEL f2 ==========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            107.50 usec
PL2               0.00 dB
PL12             24.00 dB
PL13             24.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127529 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

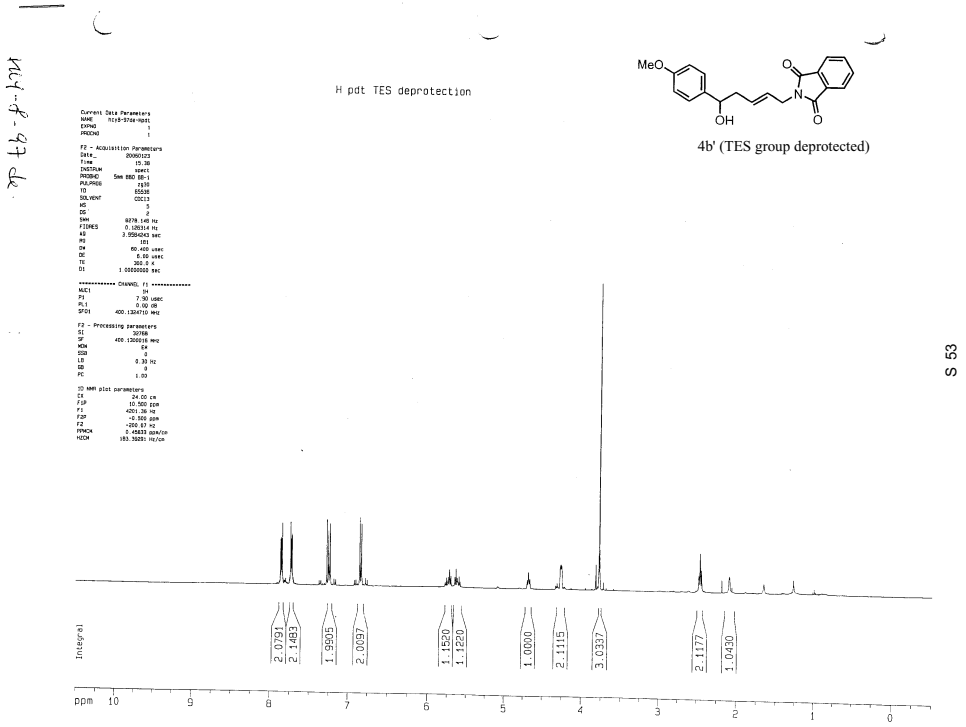
1D NMR plot parameters
CX                20.00 cm
F1P              220.000 ppm
F1             22134.80 Hz
F2P              -10.000 ppm
F2             -1006.13 Hz
PPMCM            11.50000 ppm/cm
HZCM           1157.04663 Hz/cm
```


A-pdt
OSiEt3
MeO
4b
Integral
2.0071
2.0475
2.0119
2.0019
1.0000
0.9959
1.0060
4.0315
1.0913
1.0562
1.0771
9.2524
6.1462
ppm

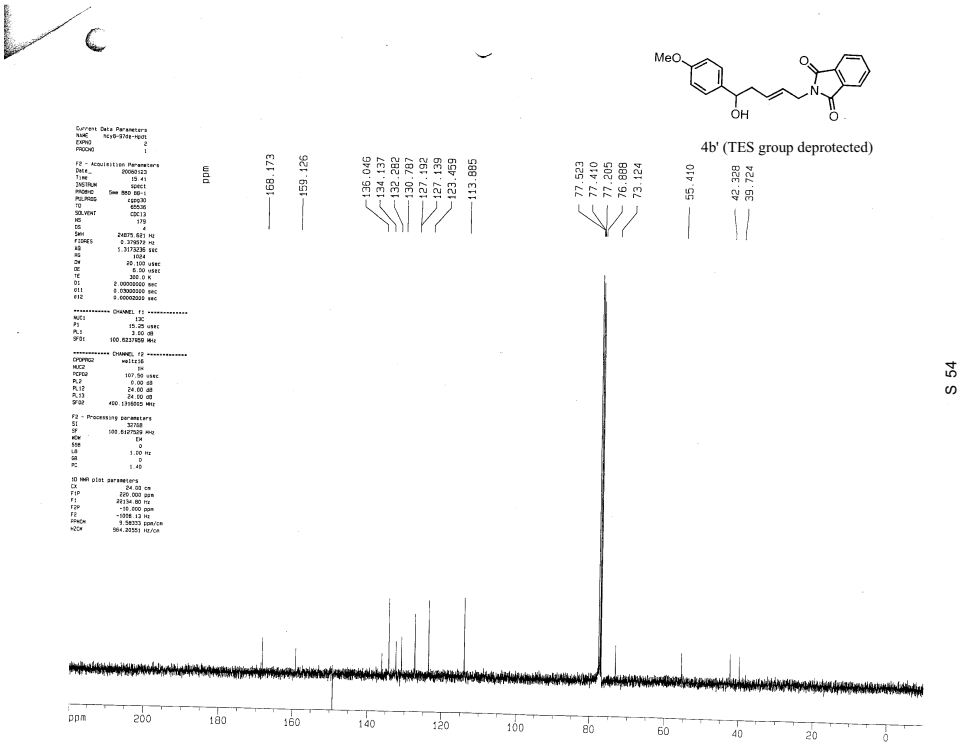
S 55


A-pdt
OSiEt3
MeO
4b
ppm
168.348
158.831
148.546
135.171
133.947
132.310
127.701
123.255
113.526
111.830
77.547
77.275
77.230
76.912
55.327
37.240
29.752
7.029
4.967

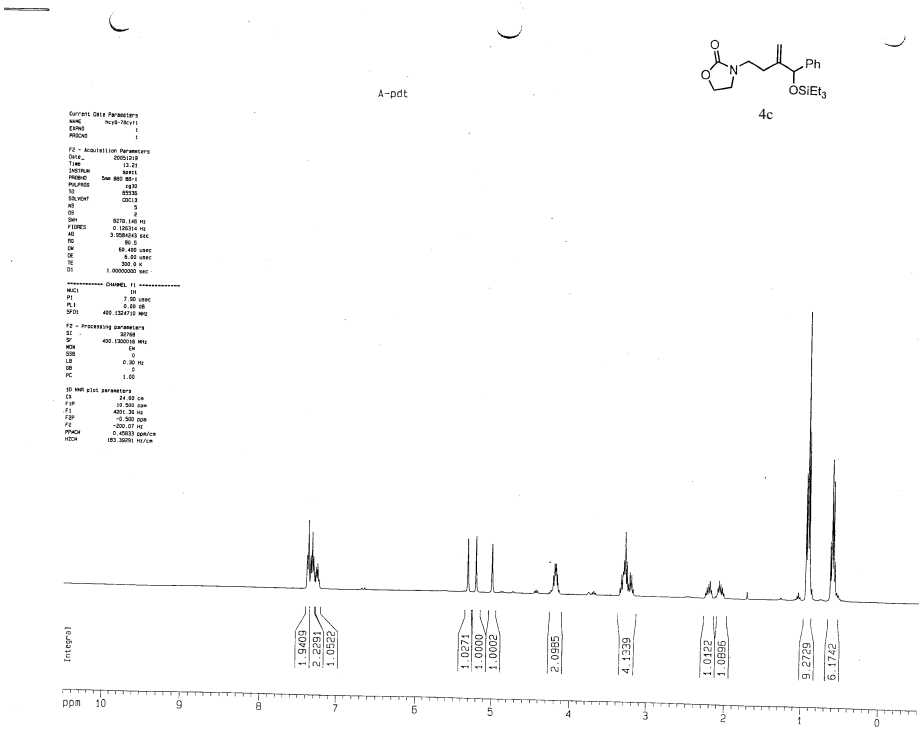
S 56

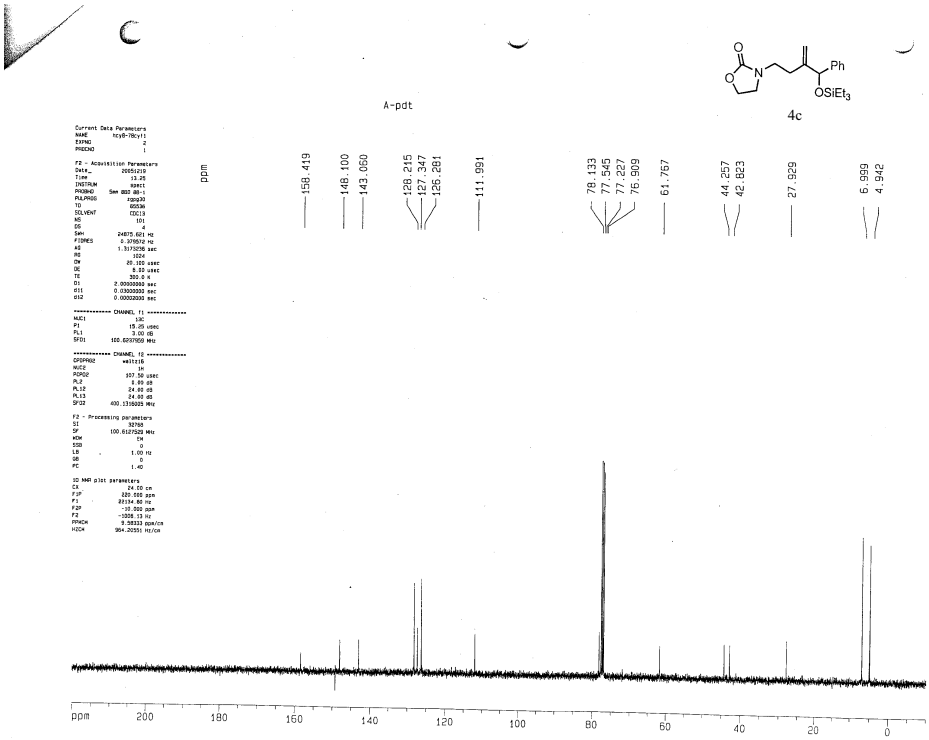

H pdt TES deprotection
MeO
OH
4b' (TES group deprotected)
Integral
2.0791
2.1483
1.9905
2.0097
1.1520
1.1220
1.0000
2.1115
3.0337
2.1177
1.0430
ppm

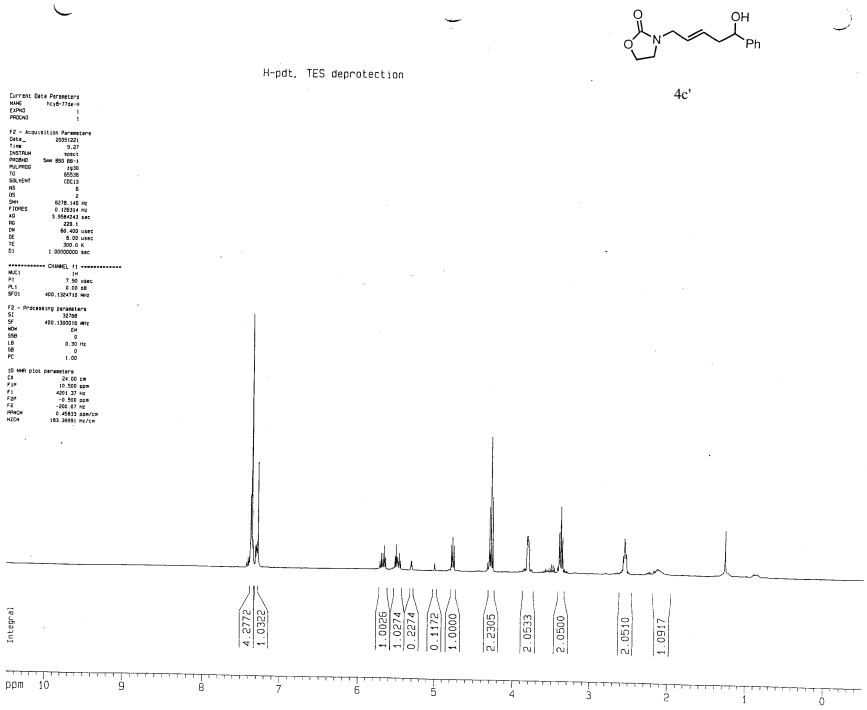
S 53

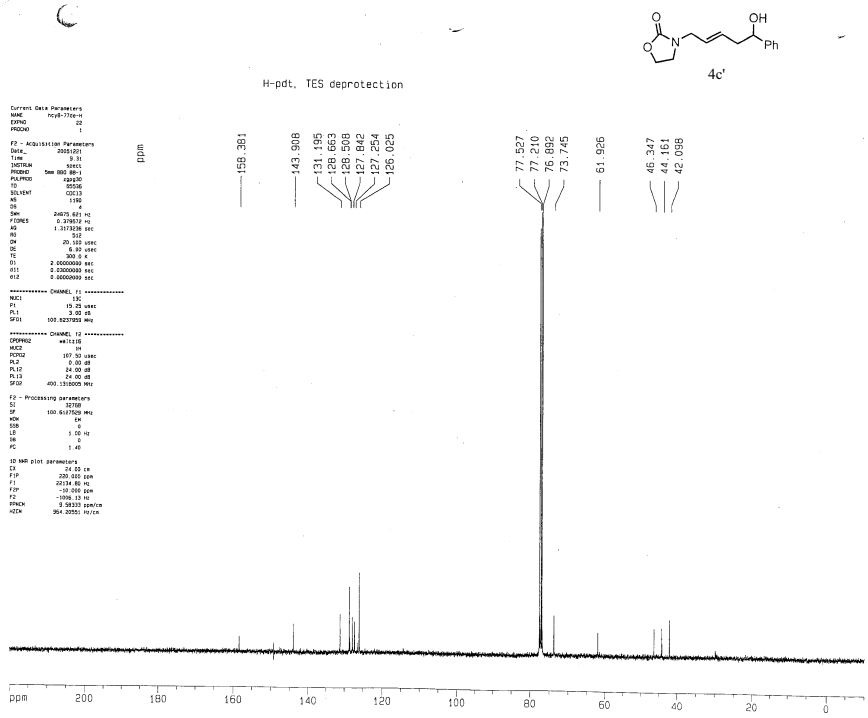

MeO
OH
4b' (TES group deprotected)
ppm
168.173
159.126
136.046
134.137
132.282
130.787
127.192
127.139
123.459
113.885
77.523
77.410
77.205
76.888
73.124
55.410
42.338
39.724

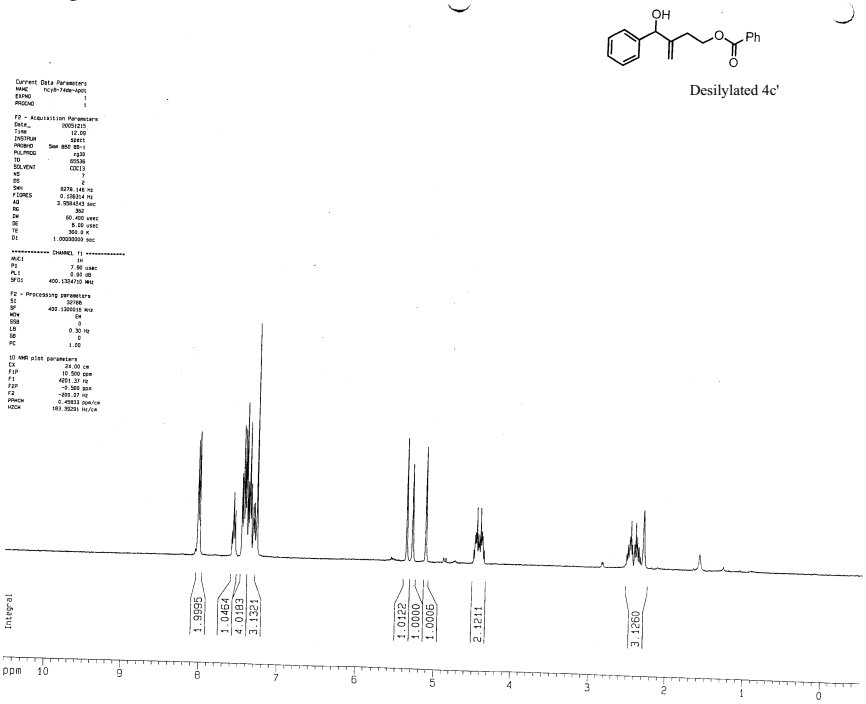
S 54

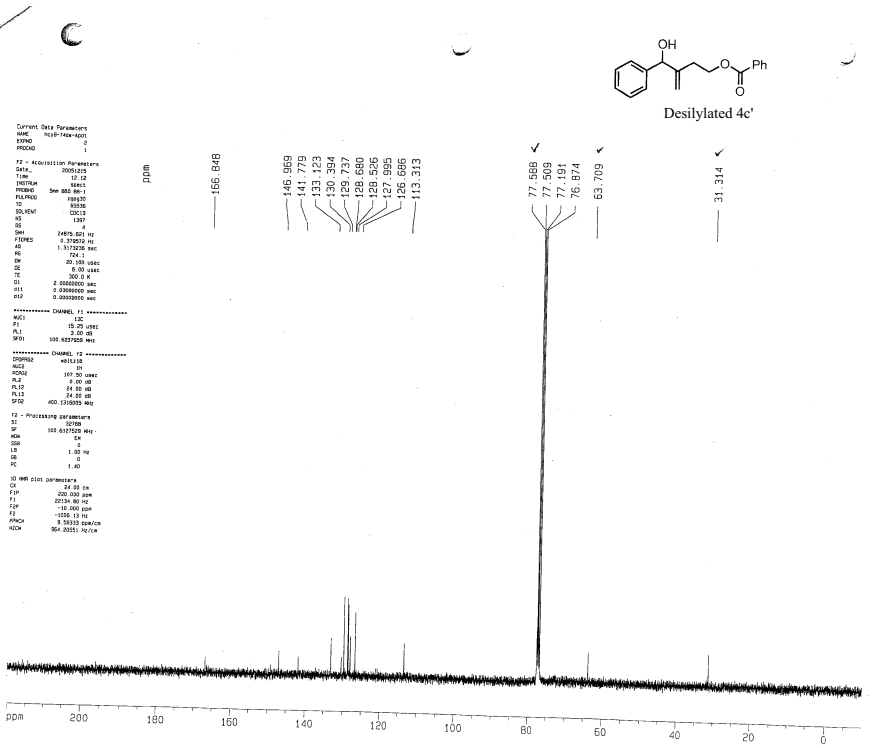

A-pdt
Ph
OSiEt3
4c
Integral
1.9409
2.2911
1.0522
1.0271
1.0000
1.0002
2.0965
4.1339
1.0122
1.0896
9.2729
6.1742
ppm


A-pdt
Ph
OSiEt3
4c
ppm
158.419
148.100
143.060
128.215
127.347
126.281
111.991
78.133
77.545
77.227
76.909
61.767
44.257
42.823
27.929
6.999
4.942

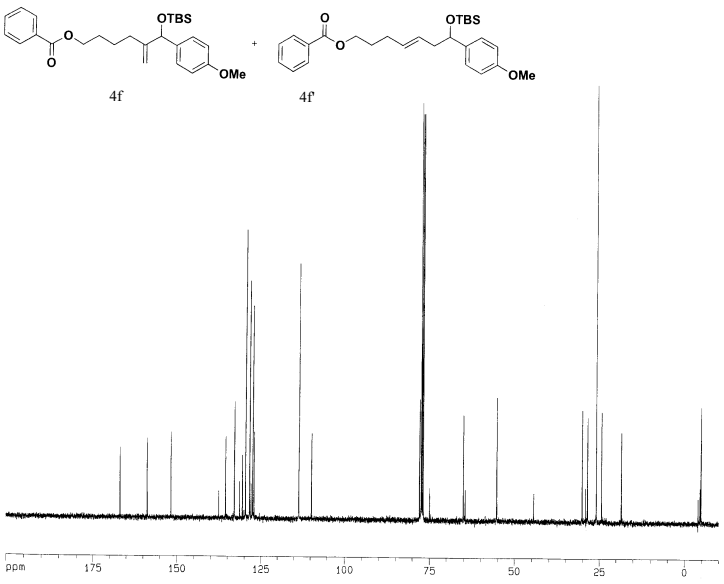

H-pdt, TES deprotection
4c'
Integral
4.2772
1.0322
1.0026
1.0274
0.2274
0.1172
1.0000
2.2305
2.0533
2.0500
2.0510
1.0917
ppm


H-pdt, TES deprotection
4c'
ppm
158.381
143.908
131.195
128.653
128.508
127.842
127.254
126.025
77.527
77.210
76.892
73.745
61.926
46.347
44.161
42.098


OH
O
Ph
O
Desilylated 4c'
Integral
1.9995
1.0454
4.0183
3.1321
1.0122
1.0000
1.0006
2.1211
3.1260
ppm


OH
O
Ph
O
Desilylated 4c'
ppm
166.848
146.969
141.779
133.123
130.394
129.737
128.680
128.526
127.995
126.666
113.313
77.568
77.509
77.191
76.874
63.709
31.314
ppm

SN050737 allylic and ene




```
Current Data Parameters
NAME          SN736-all-C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20050728
Time              20.16
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 638
DS                   4
SWH          25125.629 Hz
FIDRES        0.383387 Hz
AQ           1.3042164 sec
RG              1625.5
DW             19.900 usec
DE              6.00 usec
TE             300.0 K
D1          2.00000000 sec
d11         0.03000000 sec
d12         0.00002000 sec

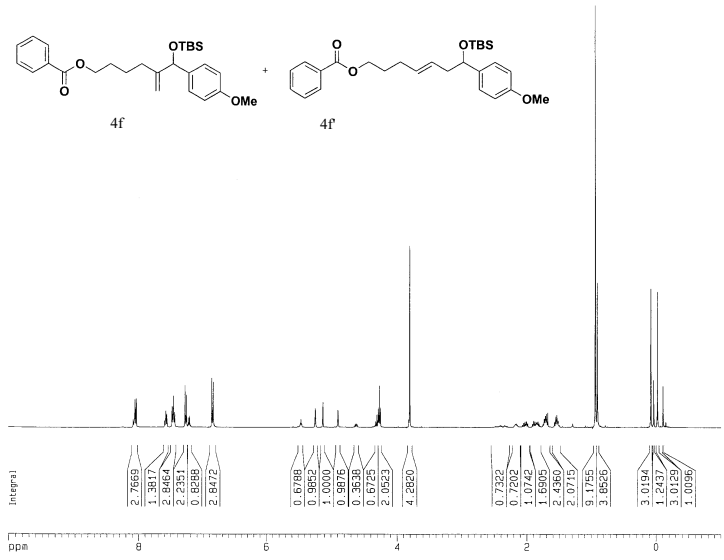
========== CHANNEL f1 ==========
NUC1              13C
P1              15.25 usec
PL1             3.00 dB
SFO1       100.6237959 MHz

========== CHANNEL f2 ==========
CPDPRG2        waltz16
NUC2              1H
PCPD2          107.50 usec
PL2             0.00 dB
PL12           24.00 dB
PL13           24.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127522 MHz
WDW                EM
SSB                 0
LB               1.00 Hz
GB                  0
PC                1.40

1D NMR plot parameters
CX               20.00 cm
F1P             200.000 ppm
F1             20122.55 Hz
F2P             -10.000 ppm
F2             -1006.13 Hz
PPMCM          10.50000 ppm/cm
HZCM        1056.43398 Hz/cm
```

SN050736 allylic and ene




```
Current Data Parameters
NAME          SN736-all-H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20050728
Time              20.11
INSTRUM           spect
PROBHD     5mm BBO BB-1
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   4
DS                   2
SWH          8278.146 Hz
FIDRES       0.126314 Hz
AQ           3.9584243 sec
RG                45.3
DW             60.400 usec
DE              6.00 usec
TE             300.0 K
D1          1.00000000 sec

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PL1             0.00 dB
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F2 - Processing parameters
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SSB                 0
LB               0.30 Hz
GB                  0
PC                1.00

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F2P             -1.000 ppm
F2             -400.13 Hz
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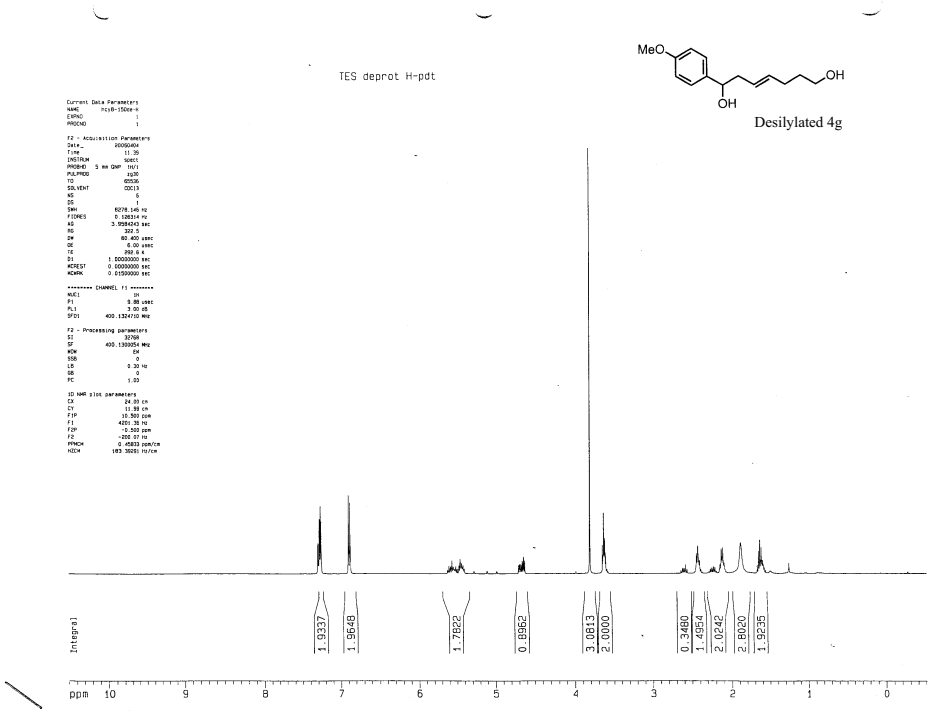
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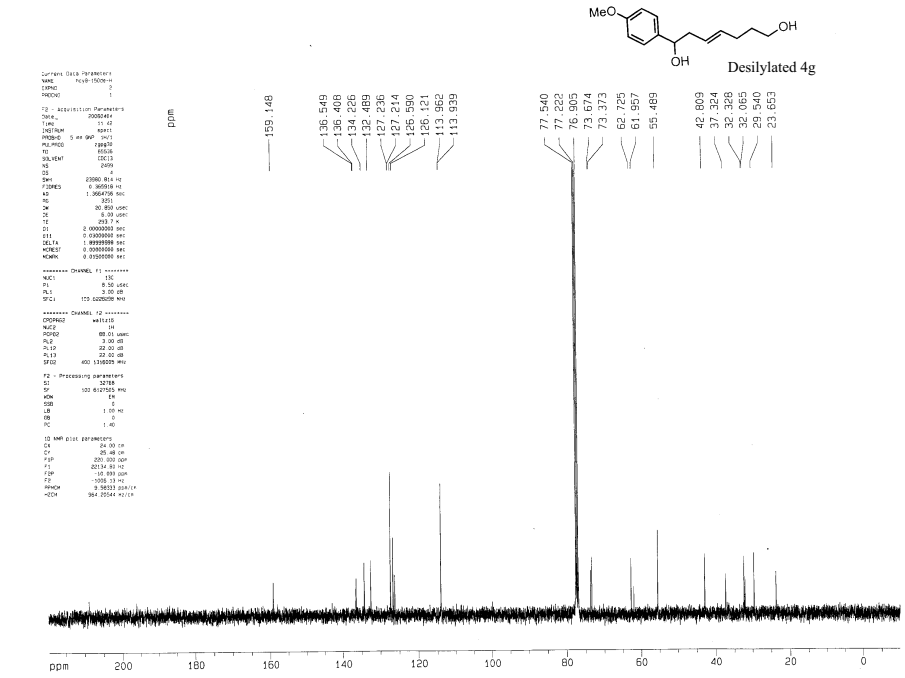
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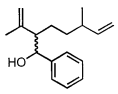

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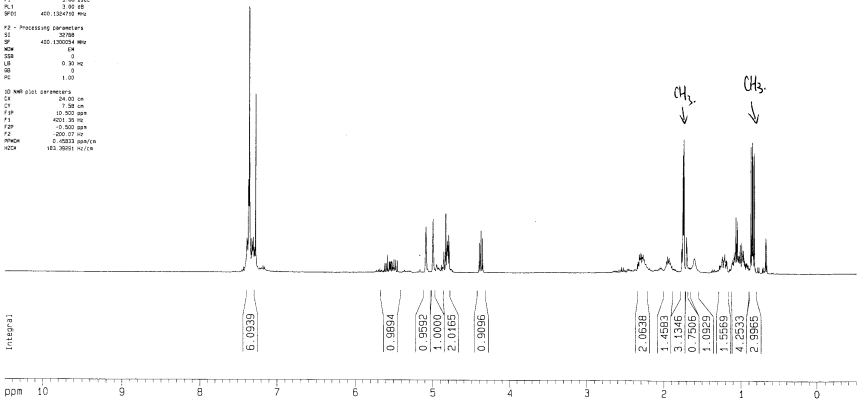

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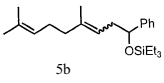

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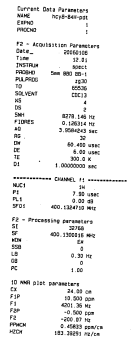

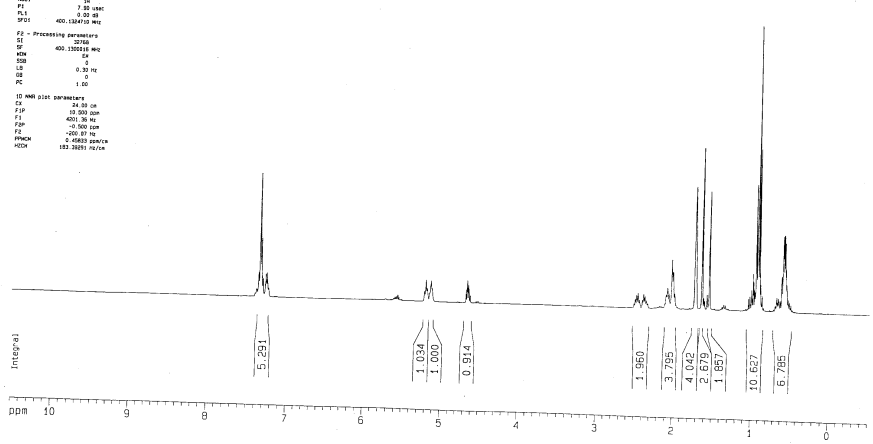

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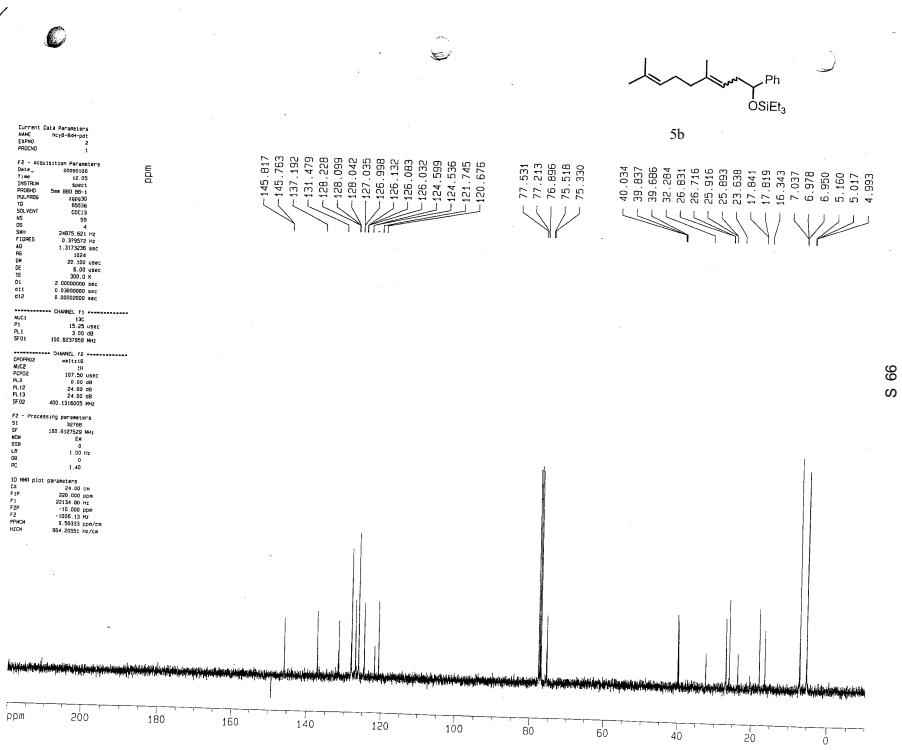
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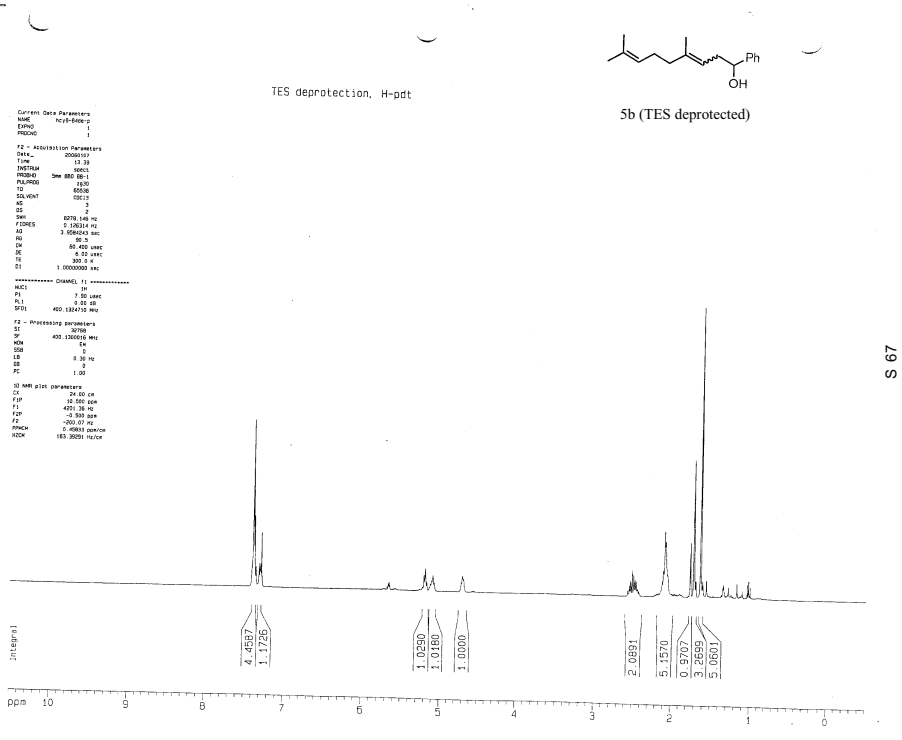
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ppm

S 67

Chapter 3

Synthetic Studies toward *ent*-Dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

Introduction

Trans-Fused Polycyclic Ether Natural Products

Trans-fused polycyclic ethers constitute an important class of marine natural products that exhibit potent biological activities.[1a,1b] Examples of these marine polycyclic ethers include brevetoxin-B and ciguatoxin, which are metabolites from dinoflagellates (Figure 1). Capable of binding to voltage-sensitive sodium channel in cell membrane and causing a sodium ion influx into cells, these macromolecules are highly neurotoxic, causing massive fish kills and human poisoning. Some polyether natural products also display anticancer properties. Protoceratin II, a yessotoxin derivative with a sugar subunit, has an IC_{50} value against human cancer cell lines of less than 0.5 nM.[1c]

These *trans*-fused polycyclic ether natural products feature a highly regular structural motif (Figure 1). Multiple five, six, seven, eight, and nine-membered cyclic ethers *trans*-fused together to create a ladder-like structure. Hence these *trans*-fused polycyclic ethers are collectively called ladder polyethers. The backbone of all ladder ethers is made up of repeating C–C–O subunits. The ring junctions throughout the macromolecular structure have a uniform *trans*-*syn*-*trans* pattern, i.e., *trans* stereochemistry across the C–C bond of each ring junction and a *syn* relationship of adjacent ring junctions. This dense but consistent array of stereocenters in ladder polyethers provides a formidable synthetic challenge.

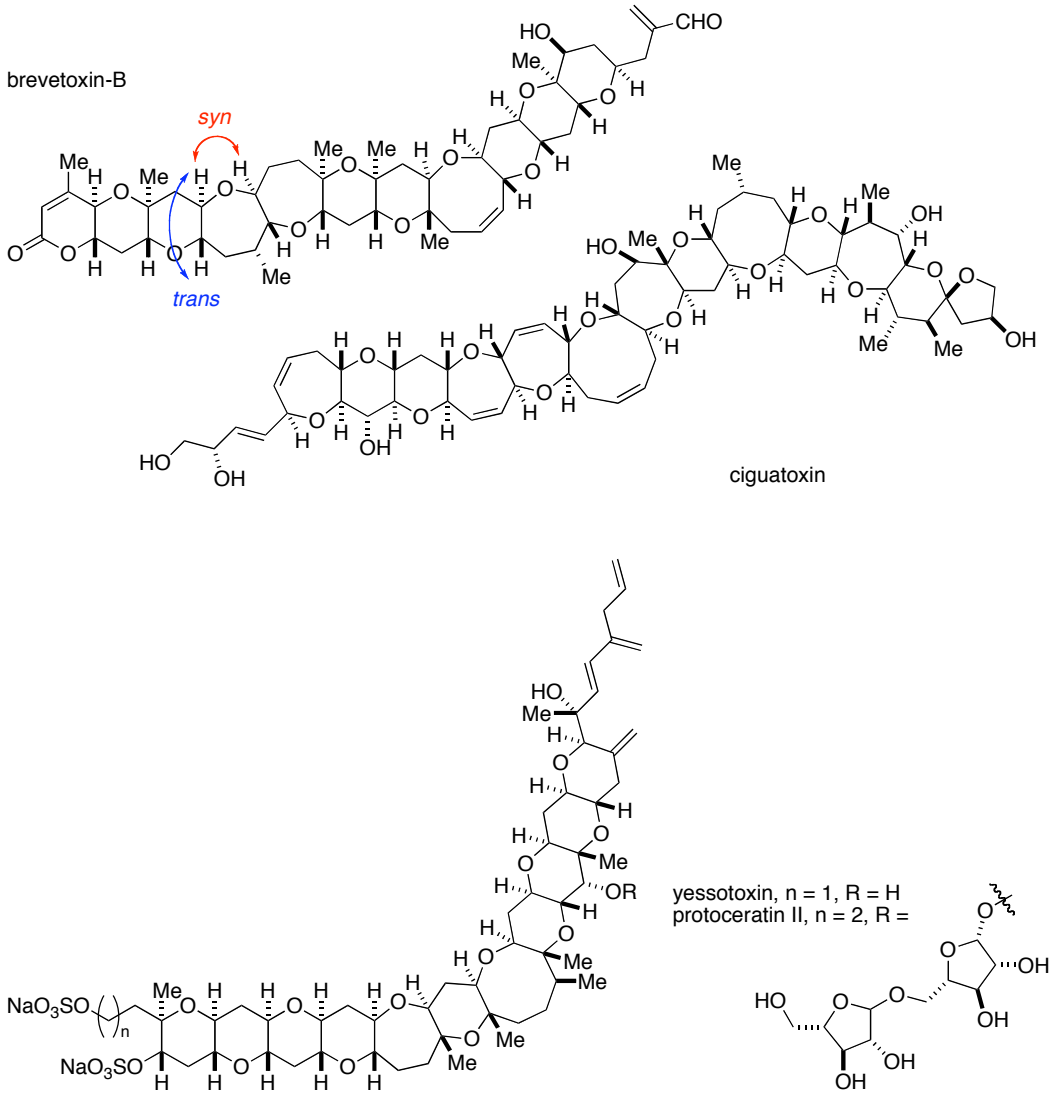


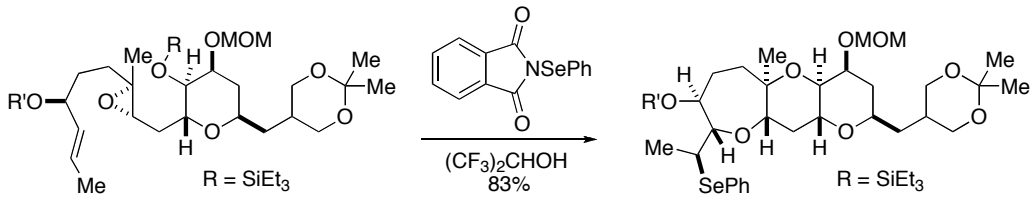
Figure 1. Examples of *trans*-fused polycyclic ether natural products.

Several total syntheses of *trans*-fused ladder ether natural products have been reported.[1a,1b] The new methods invented for the synthesis of these natural products often represented the state of the art of organic chemistry at the time the total synthesis was reported. Some of the important strategies included alkenyl group-directed cyclization of hydroxy vinyl epoxide,[1d,1e] Lewis acid-mediated allyl stannane addition to aldehydes,[1f] ring expansion reactions,[1g] selenium-induced epoxide-opening reactions,[1h] hetero-Diels-Alder reactions,[1i] samarium iodide-promoted cyclization,[1j] and ring-closing metathesis.[1i,1j]

In almost all syntheses of ladder ether natural products, one ether ring was formed at a time.[1a,1b] The only case in which more than one ether ring was created in a single step in the context of ladder polyether synthesis was Holton's synthesis of hemibrevetoxin B.[1h] *N*-(phenylseleno)-phthalimide activation of an alkene triggered formation of the 6-7 fused ring system in hemibrevetoxin B. (Scheme 1)

Scheme 1

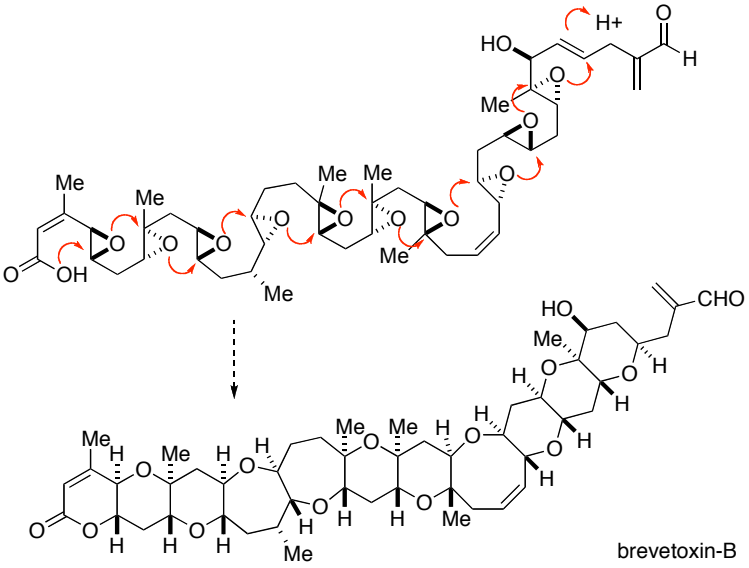
Holton:



Synthesis of Fused Polycyclic Ether from Epoxide-Opening Cascades

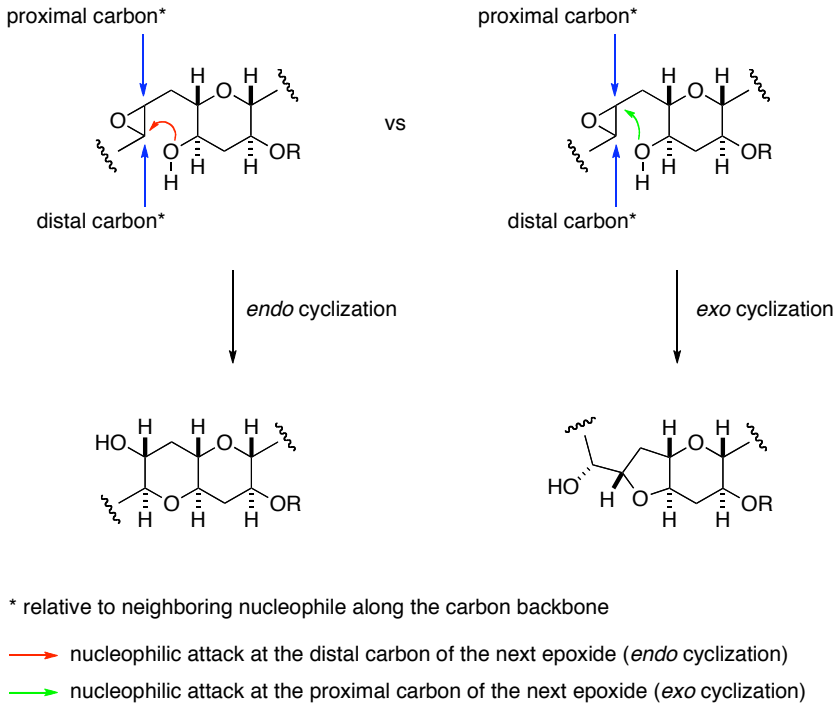
Nakanishi proposed that the biosynthesis of ladder polycyclic ether natural products proceeds via a cascade of epoxide-opening events.[2] That is, a polyepoxide undergoes several consecutive and regioselective ring-opening events to yield *trans*-fused polycyclic ether natural product (Scheme 2). None of the total syntheses of marine fused polycyclic ethers reported to date has applied this strategy.

Scheme 2



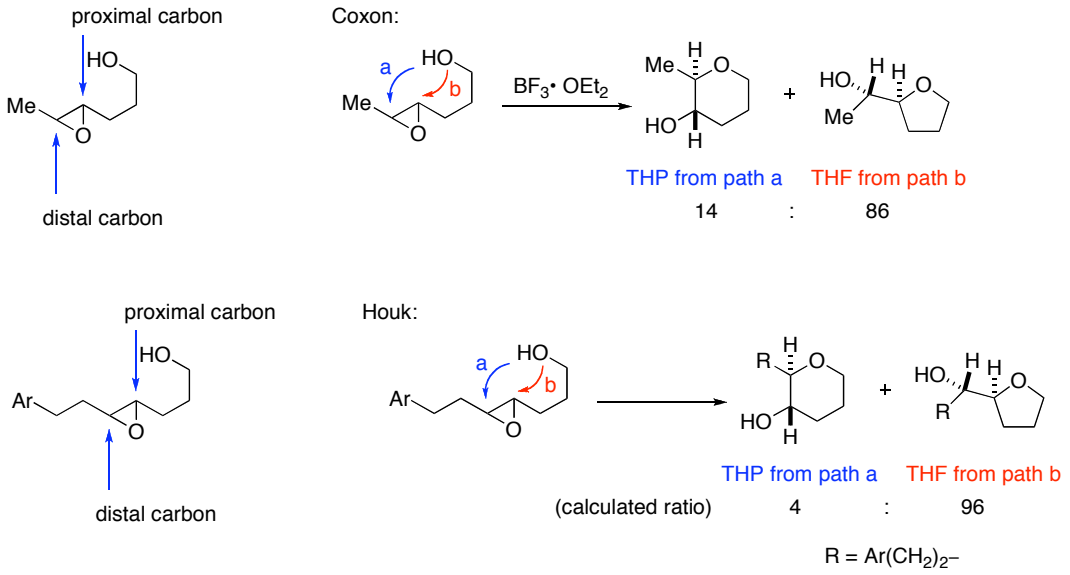
One major challenge of carrying out the Nakanishi proposal is the regioselective opening of every epoxide. Specifically, each epoxide needs to open the distal carbon of the next epoxide along the carbon backbone in order to create a fused cyclic ether system. (Scheme 3) This mode of cyclization is commonly termed *endo* cyclization. Very often, however, epoxide-opening at the proximal carbon of the next epoxide (*exo* cyclization) is a major competing reaction. The terms *exo* cyclization and *endo* cyclization, originated from the Baldwin's rule,[3a] were commonly used to describe the regioselectivity of epoxide-opening reactions. However, since both C–O bonds of the epoxide are outside the ring that will be formed after the cyclization, both modes of cyclization described in Scheme 3 can be defined as *exo* cyclization, according Baldwin's interpretation.[3a] To avoid confusion, the *exo* / *endo* terminology will not be used in the following text.

Scheme 3



An early study of an intramolecular epoxide-opening reaction on a simple system by Coxon suggested that epoxide-opening at the proximal carbon predominated with disubstituted epoxides to yield a THF product over a THP product (Scheme 4).[3b] Ab-initio calculations at the MP2 level by Houk seemed to agree with this preference.[3c] The energy difference between THF formation and THP was calculated to be ~1.9 kcal/mol, corresponding to a 96:4 selectivity, favoring THF formation at room temperature (Scheme 4). In certain cases, this selectivity can be reversed with an appropriate external influence, such as antibodies[3d] or an appropriate Lewis acid catalyst.[3e,3f] Alternatively, replacing the alkyl group on the distal carbon of a disubstituted epoxide with an alkenyl group can also lower the activation energy of a six-membered transition state.[1d,1e]

Scheme 4



Different functional groups have been installed on epoxides to bias regioselectivity in epoxide-opening cascades (Scheme 5). These functional groups are collectively called directing groups. Murai demonstrated such a cascade using epoxides with a methoxymethyl group as the directing group, to form the desired *trans*-fused polycyclic ether product.[4] McDonald and Floreancig have used methyl-substituted epoxides in epoxide-opening cascade.[5,6] None of these directing groups are common in ladder ether natural products, hence limiting their utility in synthesis.

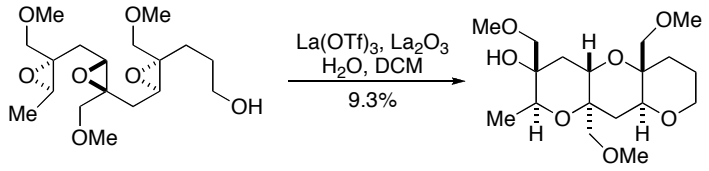
In a search for a removable directing group, Jamison has reported the use of a trimethylsilyl group as a directing group for epoxide-opening cascades (Scheme 6).[7a] Surprisingly, the fused cyclization product obtained at the end of the cascade had no trimethylsilyl group attached, and afforded fused-THP tetrad unit present in the majority of the ladder ether natural products. Thus, the trimethylsilyl group in effect acted as a "disappearing directing group".

Furthermore, Jamison also reported that attaching a tetrahydropyran to a triepoxide unit allowed very selective epoxide-opening at the distal carbon of each epoxide without the use of

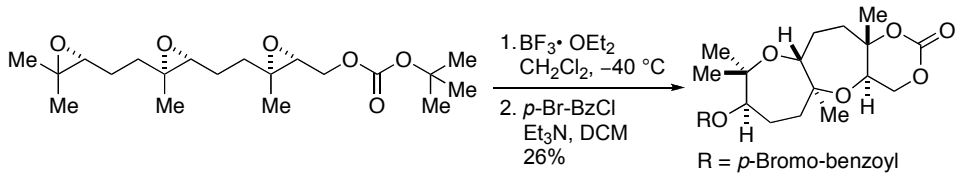
any directing group.[7b] (Scheme 6) The use of a tetrahydropyran as a template to direct epoxide-opening cascades in water closely mimicked the biosynthesis of ladder ethers that Nakanishi proposed more than 20 years ago.

Scheme 5

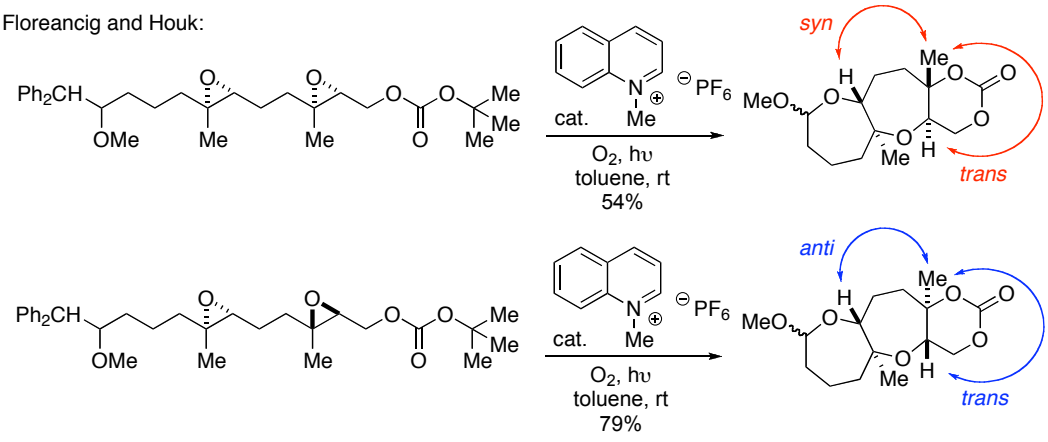
Murai:



McDonald:

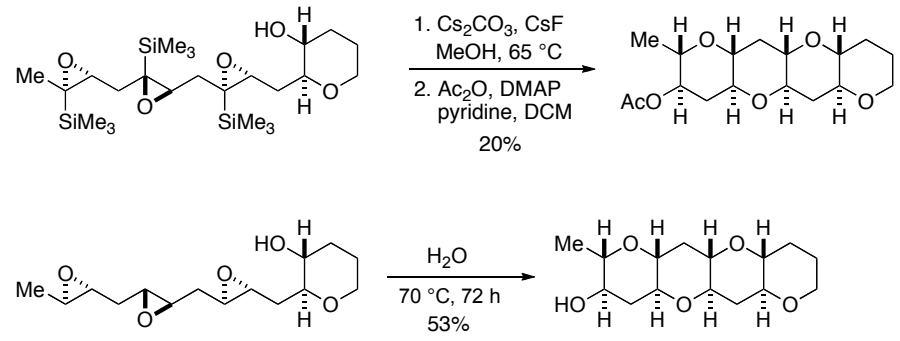


Floreancig and Houk:



Scheme 6

Jamison:



Dioxepandehydrothyrsiferol

To demonstrate the use of epoxide-opening cascades as an efficient strategy in the synthesis of fused-polycyclic ether natural products, we became interested in a fused polycyclic ether isolated from red algae *Laurencia viridis*. Dioxepandehydrothyrsiferol (**1**) is a one of the many polycyclic ether secondary metabolites isolated from this red algae (Figure 2).[8a] The repeating methyl groups suggested that **1** and other cyclic ethers isolated from *Laurencia viridis* are squalene-derived. Biological assays have shown that these polycyclic ethers are mild protein phosphatase inhibitors.[8b] While *Laurencia viridis* is a prolific source of squalene-derived polyethers, other squalene-derived polyethers such as glabresol,[9a,9b] armatol A,[10] and many others have been isolated from other sources.[11]

Similar to ladder polyethers such as brevetoxin B, **1** is characterized by an extensive fused ring system. An epoxide-opening cascade has been proposed for its biogenesis.[8a] Whether or not **1** is prepared by Nature in this fashion, synthesis following this strategy would clearly offer a

significant simplification of the challenges it present. In this vein, glabresol was synthesized by Corey using an epoxide-opening cascade.[9a]

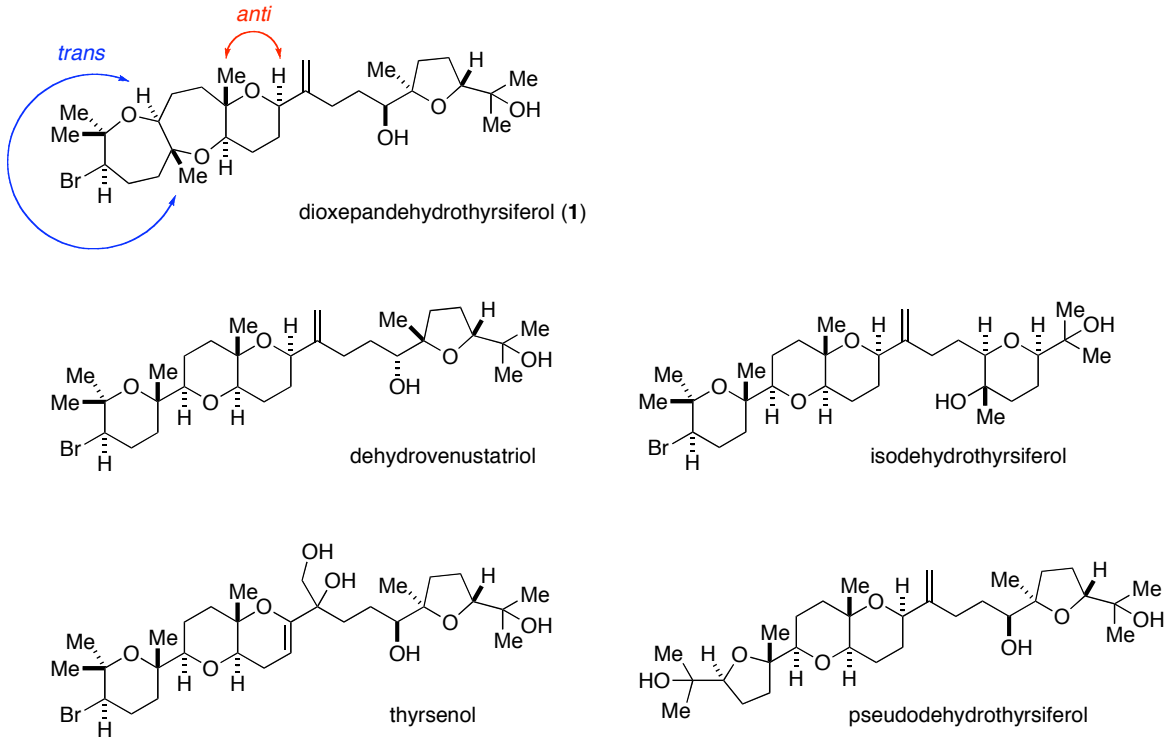


Figure 2. Dioxepandehydrothyrsiferol (**1**) and other examples of polyether metabolites from *Laurencia viridis*.

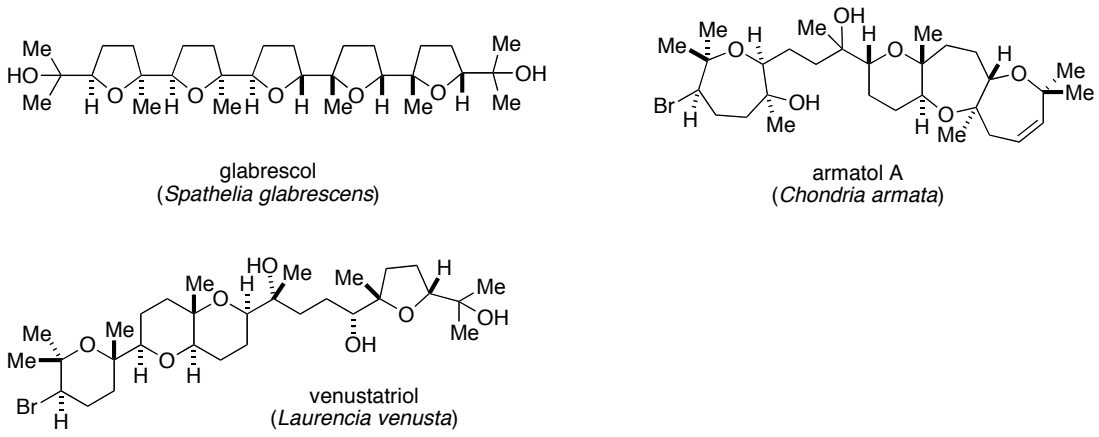
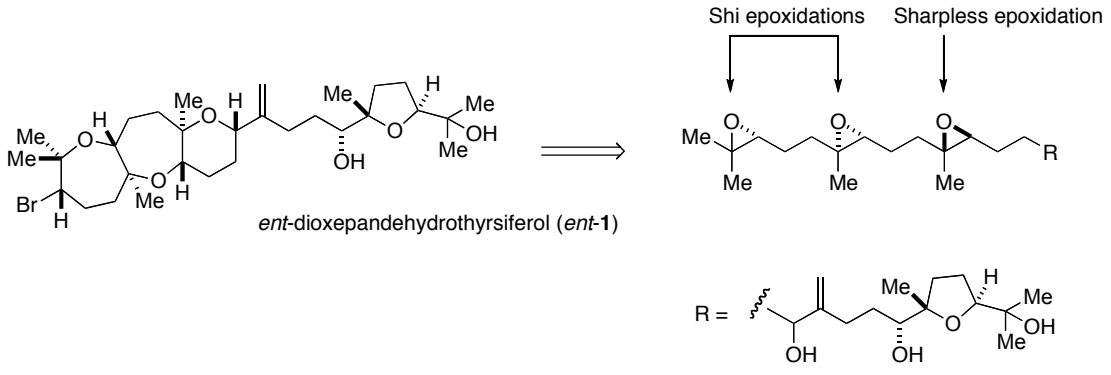


Figure 3. Examples of squalene polyethers isolated from other species.

Dioxepandehydrothyrsiferol (**1**) has structural feature different from most other fused polycyclic ether natural products. It has *trans-anti-trans* ring junctions throughout the fused ring system (Figure 2), rather than the *trans-syn-trans* junctions in all other known fused polycyclic ether natural products. Although a X-ray crystal structure was not available for dioxepandehydrothyrsiferol (**1**), NOSEY experiments[8a] and comparison to venustatriol from *Laurencia venusta*[8c] suggest that the *trans-anti-trans*-configuration would most likely cause the tetrahydropyran ring to adopt a boat structure.[8d]

Most synthetic efforts toward fused polycyclic ethers have focused on developing strategies to create a *trans-syn-trans* ring systems. One of the goals toward the synthesis of dioxepandehydrothyrsiferol (**1**) therefore is to determine whether epoxide-opening cascade can produce fused polycyclic ether with *trans-anti-trans* junctions, and whether the cascade can accommodate formation of the strained tetrahydrofuran ring in this natural product.

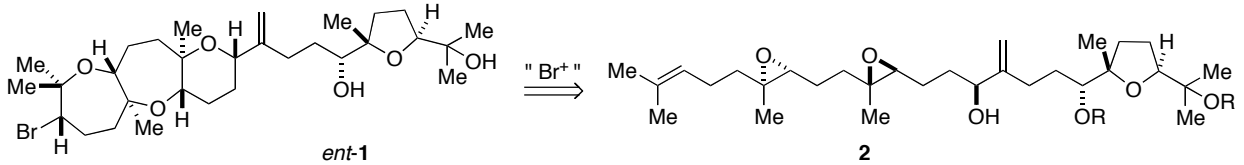
ent-Dioxepandehydrothyrsiferol (*ent*-**1**) was targeted in this study rather than the natural configuration because the more readily available enantiomer of the Shi ketone for asymmetric epoxidation (derived from natural fructose) could be used. Therefore, the discussion below will be based on *ent*-**1**.



Synthesis of ent-Dioxepandehydrothyrsiferol via an Epoxide-Opening Cascade

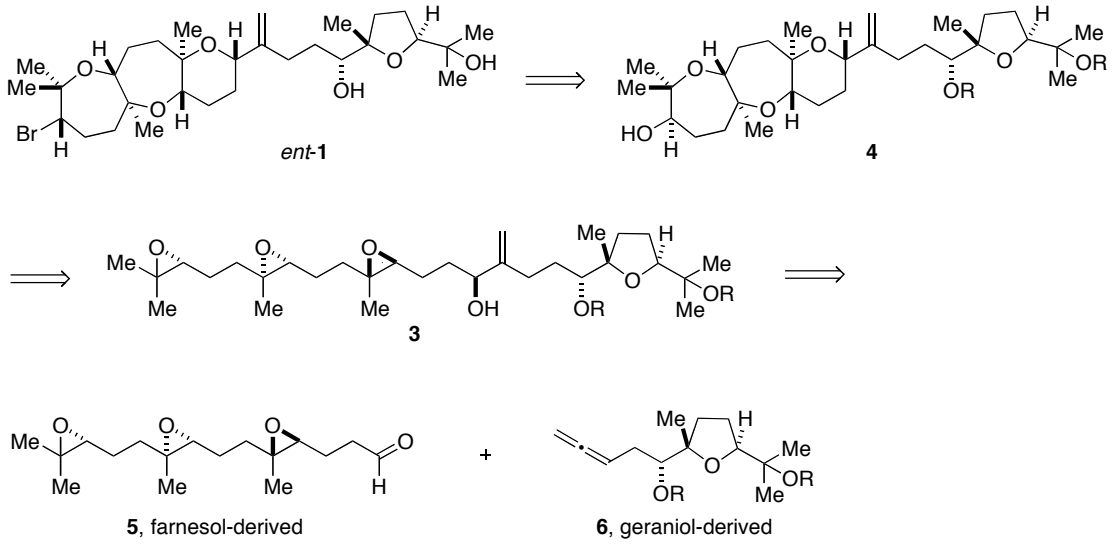
The most direct cascade that addresses the above goal would be a bromonium-initiated cascade of a diepoxide allylic alcohol such as **2** (Scheme 7). However, due to the need to protect the terminal trisubstituted alkene during the installation of epoxides onto other alkenes, synthesis of this substrate would need as many steps as an iterative synthesis. This reduces the appeal of using an epoxide-opening cascade to synthesize *ent*-**1**.

Scheme 7



An alternative cascade substrate that can be prepared in a shorter sequence would be triepoxide allylic alcohol **3** (Scheme 8). A Lewis acid-catalyzed epoxide-opening cascade should direct epoxide-opening at the more substituted carbon of each epoxide and provide the fused tricyclic ether system **4**. Bromine displacement of a leaving group derived from the alcohol with inversion would install the bromine atom without a bromonium-initiated cascade.[9c-9g] The triepoxide allylic alcohol substrate (**3**) also provides an opportunity to apply a nickel-catalyzed allene–aldehyde coupling as described in Chapter 1. The required aldehyde (**5**) and allene (**6**) could be prepared from farnesol and geraniol respectively.

Scheme 8



Fused six-seven-seven ring structures similar to the one in *ent*-**1** have been prepared by epoxide-opening cascades using two different initiation methods (Scheme 5). McDonald used Lewis acid to activate epoxides for cascade cyclization, while Floreancig initiated an epoxide-opening cascade with an oxocarbenium ion generated by the oxidative removal of a diphenylmethyl group. Floreancig's examples also demonstrated that either *syn* or *anti* ring junctions can be formed through a cascade cyclization. Common to all known literature examples of successful epoxide-opening cascade with methyl substituted epoxides are the use of carbonate, carbamate, and ester as the terminating nucleophiles.[12] Other terminating nucleophiles such as secondary alcohols have been used in other epoxide-opening cascades to prepare for example fused-THF tetrad with *trans-syn-trans* junctions (Scheme 6). All of the pyran rings in the fused poly-THP adopt the chair conformation. There are, however, no known epoxide-opening cascade using a secondary alcohol as the terminating nucleophile to form a THP ring that has a boat conformation, as would be the case in *ent*-**1**.

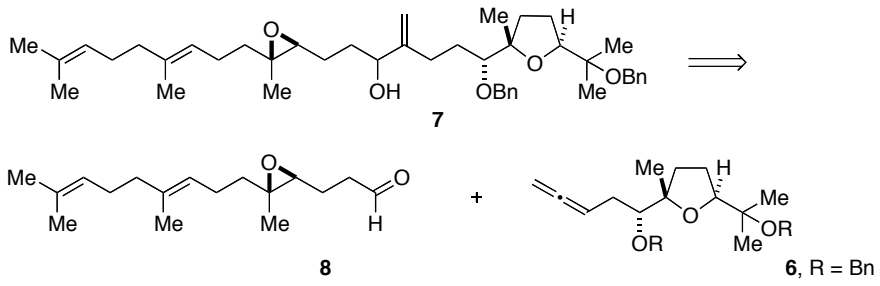
The THP ring in *ent*-**1** is not in a chair conformation because the methyl group and the alkenyl group of the THP ring are *syn* to each other. It was not clear from known examples of epoxide-opening cascades that the proposed cascade in Scheme 8 would proceed as desired due to the strained THP ring in *ent*-**1**. Therefore the synthetic study of *ent*-**1** began with an evaluation of reaction conditions to form the strained THP ring.

Evaluation of Epoxide-Opening Substrates

Screening of Epoxide-Opening Reactions by 2° Allylic Alcohols

Epoxy allylic alcohol **7** was prepared to investigate the formation of the THP ring in *ent*-**1** (Scheme 9). To avoid premature epoxide-opening reaction during the synthesis of this substrate, a nickel-mediated coupling of allene **6** and aldehyde **8** was utilized.

Scheme 9

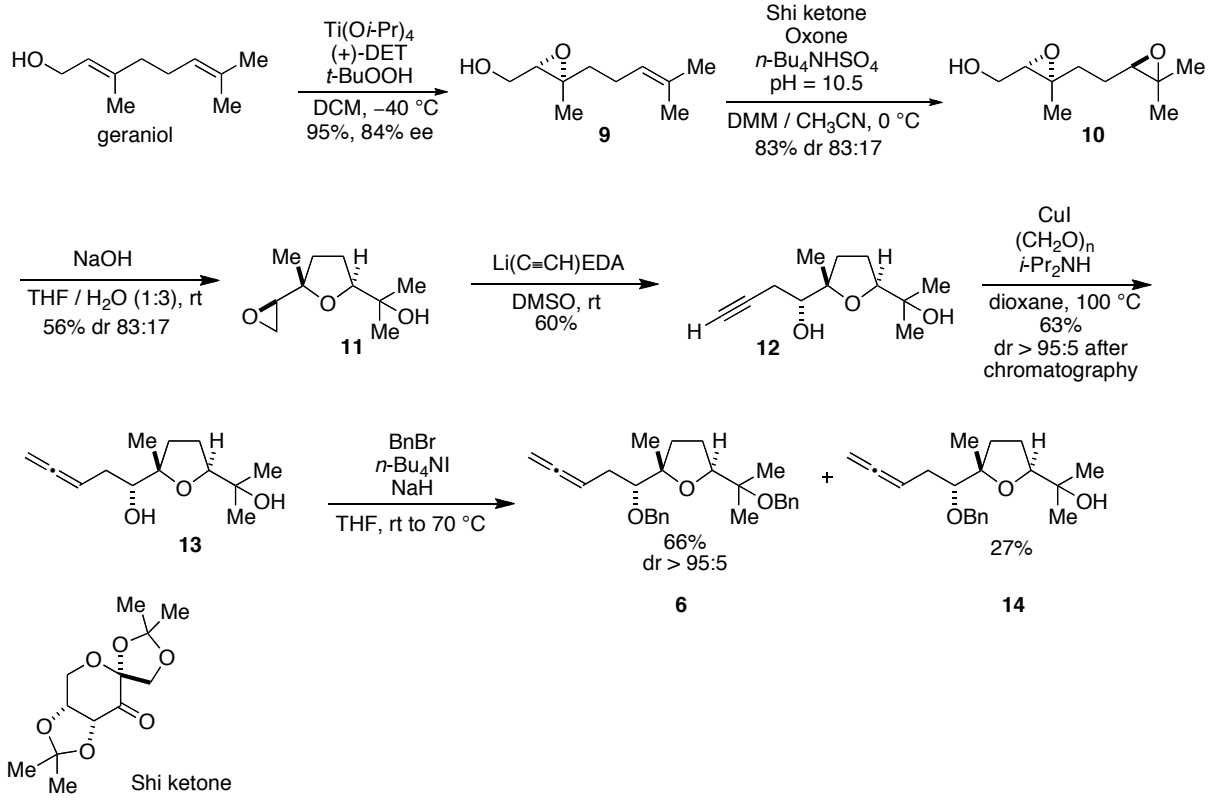


Allene **6** was prepared in six steps from geraniol (Scheme 10). Sharpless asymmetric epoxidation on geraniol,[13] followed by a Shi asymmetric epoxidation furnished epoxy alcohol **10** with a diastereomeric ratio (dr) of 83:17.[14] The dr and ee of **10** could be enhanced by recrystallization of the *p*-nitrobenzoate derivative of alcohol **10**. Alternatively, the mixture of diastereomers could be carried on and separated in subsequent steps. Payne rearrangement of alcohol **10** provided epoxide **11**,[15] which was opened with lithium acetylide to alkyne **12**. The

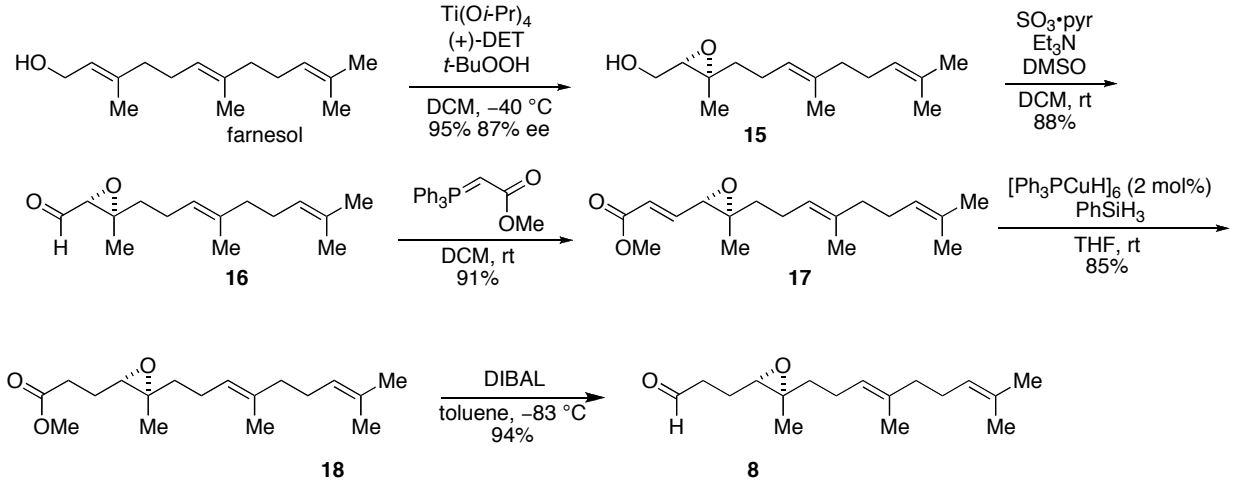
alkyne was converted to allene **13** by a Crabbé homologation reaction.[16] The two alcohols on allene **13** were protected as benzyl ethers to give allene **6**.

Aldehyde **8** was prepared using a slightly modified method from Corey (Scheme 11).[20f] Sharpless asymmetric epoxidation of farnesol followed by a Parikh-Doering oxidation provided epoxy aldehyde **16**. Wittig olefination of aldehyde **16** furnished enoate **17** as a mixture of *cis* and *trans* isomers. Conjugate reduction of enoate **17** was best achieved with phenylsilane and a catalytic amount of Stryker reagent to prevent opening of the sensitive alkenyl-epoxide.[17] The resulting ester **18** was reduced to aldehyde **8** by DIBAL.

Scheme 10

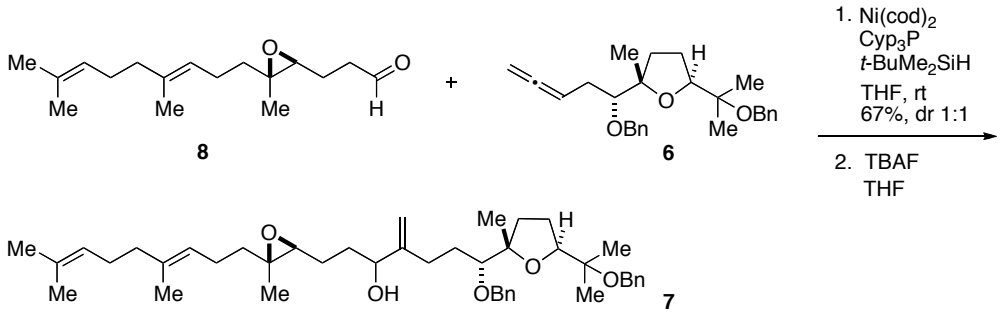


Scheme 11



Allene **6** and aldehyde **8** was coupled in the presence of stoichiometric $Ni(cod)_2$ and *tert*-butyldimethylsilane to provide the desired allylic ether as a 50:50 mixture of diastereomers (Scheme 12).[18] The silyl group was removed by TBAF to provide epoxy allylic alcohol **7** for cyclization studies.

Scheme 12



The two diastereomers of epoxy alcohols (*R*)-**7** and (*S*)-**7** (as a 50:50 mixture, the only difference being the configuration of the allylic alcohol stereocenter) were subjected to a wide variety to Brønsted and Lewis acids to induce cyclization (Scheme 13). Four different cyclization products could be identified. Epoxide opening at the more substituted carbon (the distal carbon) of the epoxides yielded two THP rings (*syn*-THP (*R*)-**20** and *anti*-THP (*S*)-**20**), one from each

diastereomer. Epoxide-opening at the less substituted carbon (the proximal carbon) of the epoxides yielded two THF rings (*syn*-THF (*S*)-**20** and *anti*-THF (*R*)-**20**), also one from each diastereomer. The *anti*-THP product from the (*S*)-**7** was the desired product for the synthesis of *ent*-**1**. The THP:THF ratio in the cyclization of epoxy alcohol **7** appeared to depend on the configuration of the allylic alcohol (Table 1).

Scheme 13

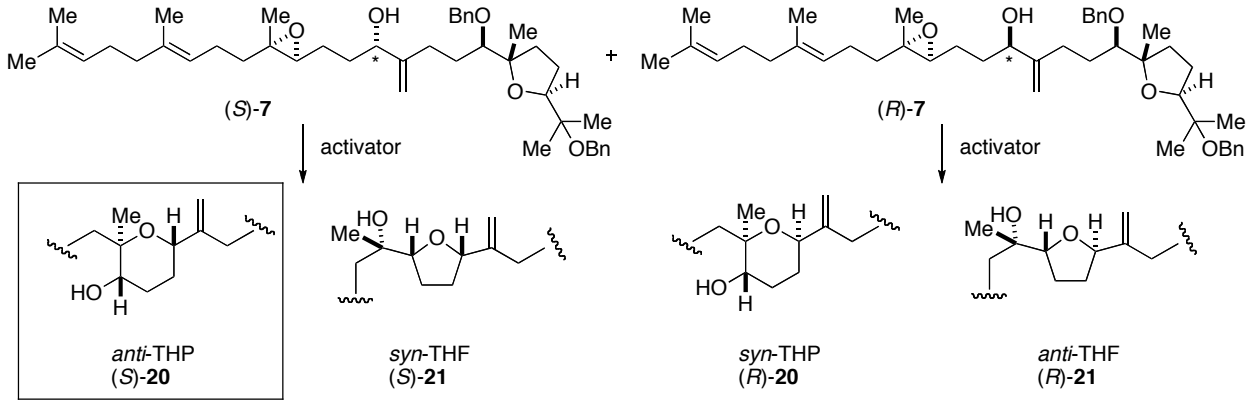


Table 1. Cyclization Screen of Epoxy alcohol **7**

entry[a]	activator	temperature (°C)	(S)-**7** THP:THF[b]	(R)-**7** THP:THF[b]
1	BF_3OEt_2	–78/–40	45:55	95:5
2	Me_2AlCl	–78/–40	7:93	95:5
3	Et_2AlCl	–78/–40	8:92	95:5
4	Me_3Al	–45/rt	95:5	65:35
5	$MgBr_2$-OEt_2	–45/rt	51:49	87:13
6	$Yb(OTf)_3$	–45/–30	11:89	90:10
7	$Sc(OTf)_3$	–45/–30	11:89	90:10
8	$Zn(OTf)_2$	–45/–30	9:91	90:10
9	$Eu(OTf)_3$	–78/rt	16:84	87:13
10	$TiCl_4$	–45/10	5:95	95:5
11	$Ti(OiPr)_4$ / BINOL	–45/rt	34:66	95:5
12	none	rt/75	15:85	71:29
13	CSA	rt	30:70	50:50
14	*N*-boc-Arg-HCl	rt	13:87	50:50

[a] Entries 1-11 were carried out in DCM. Entries 12-14 were carried out in CH_3CN. Reactions were quenched after starting material was consumed. [b] Ratios were determined by NMR.

In almost all cases (*R*)-**7** cyclized in the presence of a variety of Lewis acids to form *syn*-THP (*R*)-**20** in high preference to *anti*-THF (*R*)-**21** (Table 1, entries 1-11). Strong Lewis acid such as BF_3•OEt_2, Me_2AlCl, Et_2AlCl, $MgBr_2$•OEt_2, $TiCl_4$, Ti(O*i*-Pr)$_4$ / BINOL and various metal triflates provided greater than 85:15 THP:THF selectivity. Protic acids such as CSA and *N*-boc-arginine-

HCl were not very selective and provided ~ 50:50 mixture of *syn*-THP and *anti*-THF (entries 13-14). Using other protic acids such as PPTS, tartaric acid, TsOH, and trifluoroacetic acid gave similar results as CSA. These results suggested that under Lewis acidic conditions epoxy allylic alcohol (*R*)-**7** in general favored epoxide-opening at the more substituted carbon of the epoxide. Simple heating with no acid promoter was also more selective for THP over THF (entry 12).

The selectivity trend was very different with (*S*)-**7**. In the presence of either a Lewis acid or a protic acid the *syn*-THF (*S*)-**21** product almost always predominated over *anti*-THP product (*S*)-**20** (Table 1). The highest THP:THF selectivity was at ~50:50 using $BF_3 \cdot OEt_2$ (entry 1) and $MgBr_2 \cdot Et_2O$ (entry 5). Simple heating with no acid promoter favored the THF product (entry 12).

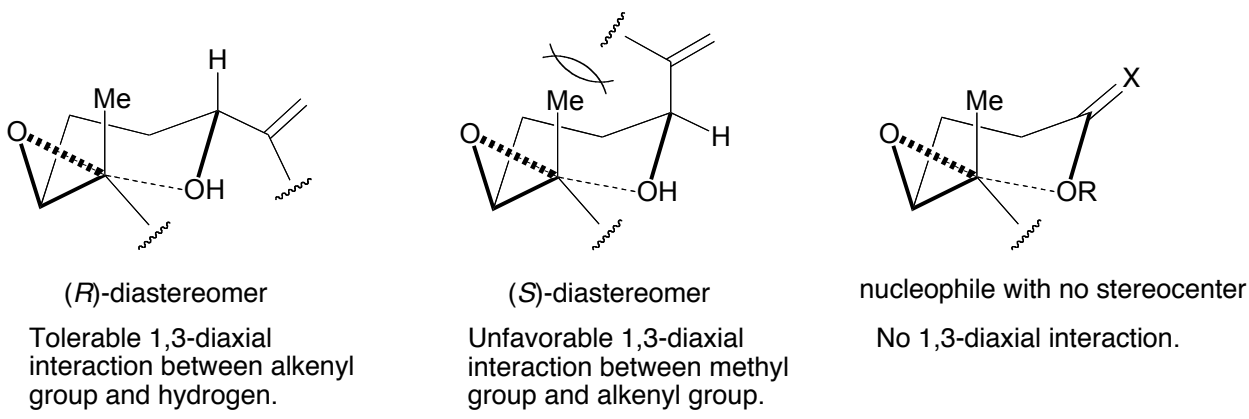
The contrasting difference in THP/THF selectivity between (*R*)-**7** and (*S*)-**7** can be accounted for using a chair transition state model to form the THP product, which has also been suggested by Forsyth (Scheme 14).[20g] When (*R*)-**7** was activated by Lewis or protic acids, partially positive charge was created at the more substituted carbon of the epoxide. The nucleophilic allylic alcohol approached the partially positive charge to form a six-membered transition state. The *R* diastereomer can accommodate both of the two larger substituents (alkenyl group of the allylic alcohol and alkyl group on the epoxide) at the equatorial positions of a chair transition state. This creates a 1,3-diaxial interaction only between a methyl group and a hydrogen atom, which is relatively tolerable. Therefore the THP is favored over the THF for (*R*)-**7**.

On the other hand, a similar chair transition state for the (*S*)-**7** would produce a severe 1,3-diaxial interaction between the methyl group of the epoxide and the alkenyl group of the allylic alcohol (Scheme 14). Therefore it is not as favorable for the (*S*)-allylic alcohol to open the

epoxide at the more substituted carbon to yield a THP ring. Opening the epoxide at the less substituted carbon becomes the lower energy pathway for the epoxide-opening reaction, yielding the THF product as the major product.

The same chair transition state model also predicts that if the 1,3-diaxial interaction between the nucleophile and the epoxide can be completely removed, a six-membered transition state should be favorable under acidic conditions and favor the formation of six-membered ring over five-membered ring product (Scheme 14). These conditions could be achieved using nucleophiles attached to sp^2-hybridized carbon atoms such as a ketone or a carboxylic acid ester.

Scheme 14

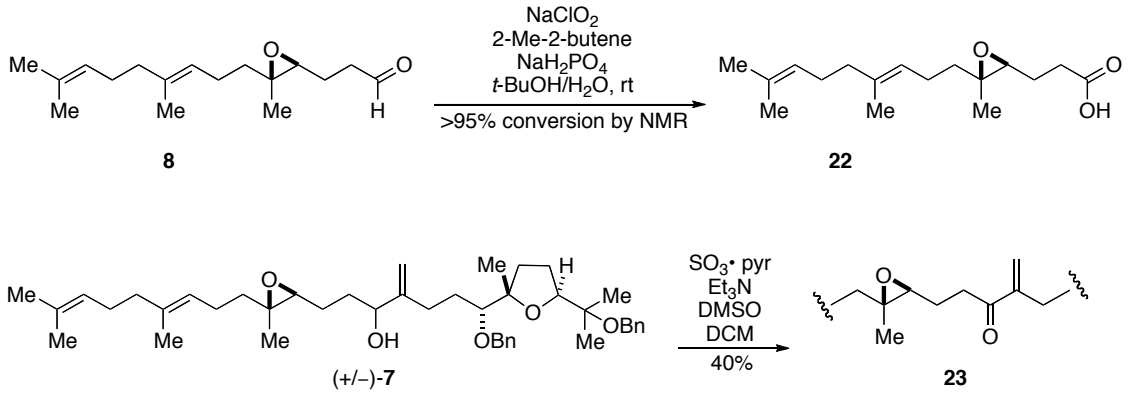


Screening of Epoxide-Opening Reactions by Nucleophiles with No Stereocenter

Two trisubstituted epoxides with nucleophiles that have no stereocenter were prepared to evaluate the regioselectivity of intramolecular epoxide-opening under acid conditions (Scheme 15). A Pinnick oxidation of γ-epoxy aldehyde **8** provided γ-epoxy carboxylic acid **22** cleanly with no premature cyclization.[19] Parikh-Doering oxidation of epoxy allylic alcohol (+/–)-**7** afforded epoxy enone **23**. Similar to the cyclization of epoxy allylic alcohol **7**, epoxide-opening at the more substituted carbon (the distal carbon) would yield a six-membered ring whereas

epoxide-opening at the less substituted carbon (the proximal carbon) would yield a five-membered ring.

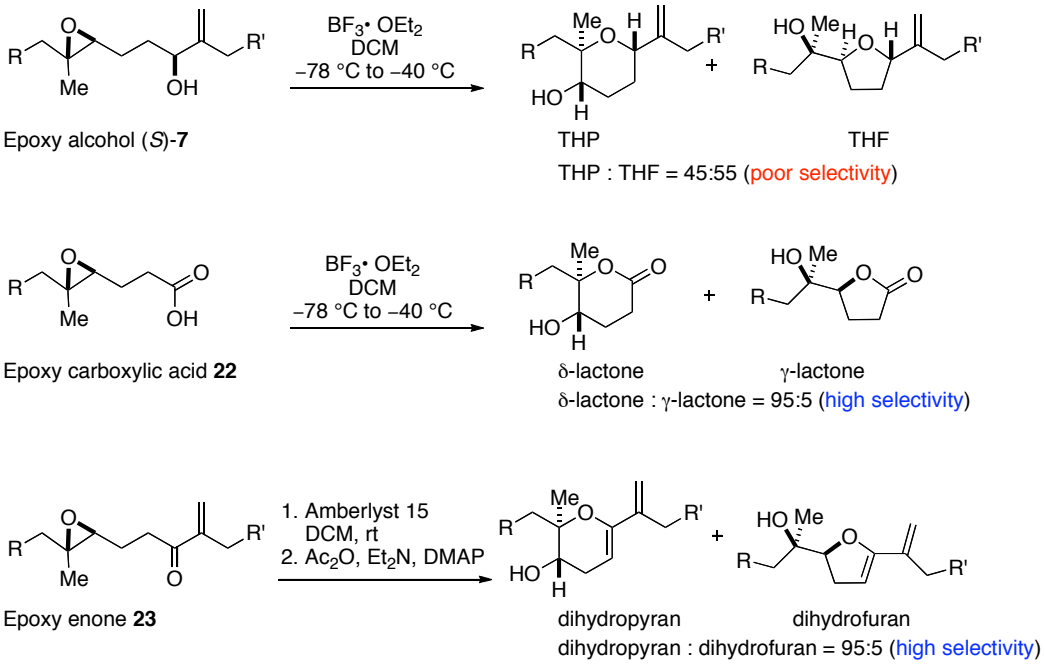
Scheme 15



Both epoxy carboxylic acid **22** and epoxy enone **23** favored the formation of six-membered rings under acidic conditions (Scheme 16). While (*S*)-**7** exhibited poor selectivity for THP over THF (45:55) using BF_3•OEt_2 as the promoter, epoxy carboxylic acid **22** displayed superior selectivity for δ-lactone over γ-lactone under the same reaction conditions (95:5). Similarly, when epoxy enone **23** was treated with Amberlyst 15 at room temperature, dihydropyran was the major cyclization product (95:5). There are also isolated examples in the literature in which other nucleophiles such as ketone,[20a,20b,20c] enol,[20d] phenol,[20e] and cyanohydrin[20f] also favored 6-membered ring over 5-membered ring in intramolecular epoxide-opening reactions.

To conclude, unless there is strong destabilization for a six-membered transition state (such as a severe 1,3-diaxial interaction), epoxide-opening occurs at the more substituted carbon of the epoxide to yield a six-membered ring product.

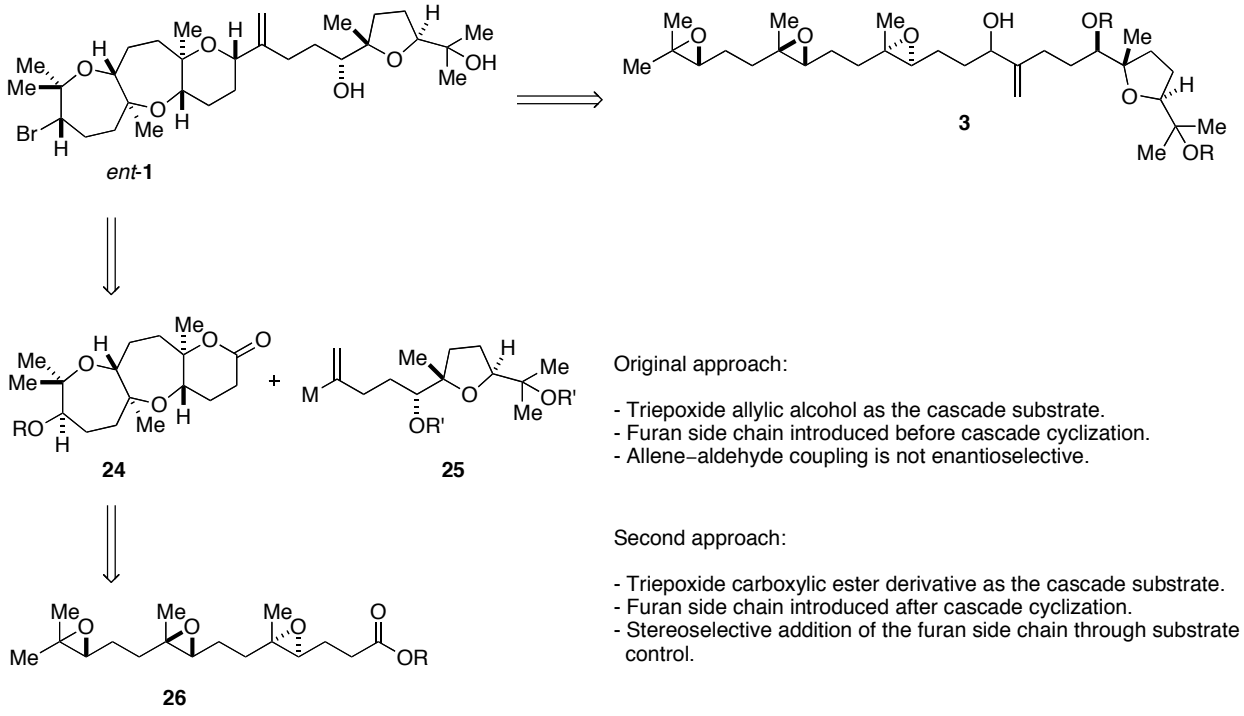
Scheme 16



Synthesis of the Tricyclic Ether Fragment via an Epoxide-Opening Cascade

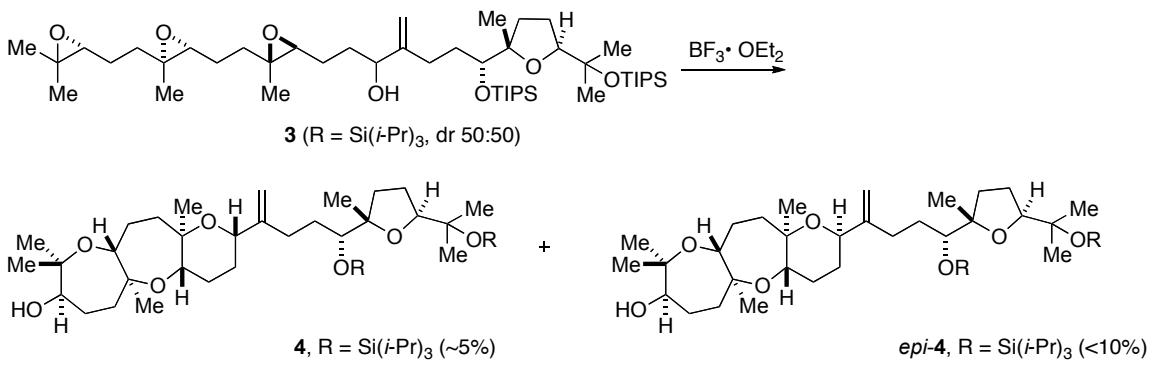
The study of nucleophile-dependent regioselectivity in the epoxide-opening reactions was extended to triepoxide substrates (Scheme 17). Hence, besides the original proposal of using triepoxide allylic alcohol **3** to obtain the fused-cyclic ether system in *ent*-**1**, a triepoxide substrate with a carboxylic acid nucleophile (**26**) was also evaluated. This second approach could be more advantageous in that the furan side chain of *ent*-**1** would be installed after the cascade cyclization. A stereoselective installation of the furan side chain might be possible by taking advantage of the conformation of the fused tricyclic ether system (**24**). On the other hand, the nickel-mediated reductive coupling approach to the triepoxide allylic alcohol substrate (**3**) was not enantioselective.

Scheme 17



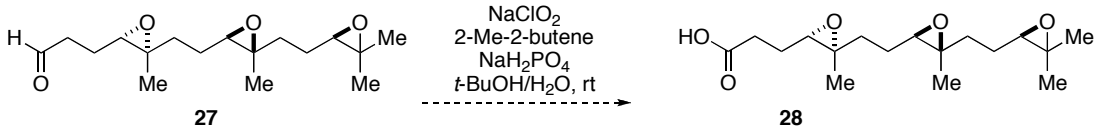
Treatment of triepoxide allylic alcohol **3**[21] with $BF_3 \cdot OEt_2$ resulted in a complex mixture of products from both diastereomers. By comparing authentic samples of **4** and *epi*-**4** prepared from an alternate route (vide infra), it can be concluded that a trace amount of the desired cyclization product (**4**) was formed (~ 5%), as well as its diastereomer *epi*-**4** (< 10%) (Scheme 18). The lower yield of alcohol **4**, as compared to the yield of *epi*-**4** seems to suggest that it is more difficult to form the THP ring in **4**.

Scheme 18



Triepoxide carboxylic acid **28** would be too sensitive to be isolated from a Pinnick oxidation of the corresponding aldehyde **27** (Scheme 19).[22] Therefore triepoxide *tert*-butylester **29** was prepared instead. The *tert*-butyl group could be removed in situ with the Lewis used in the epoxide-opening cascade (Scheme 20).

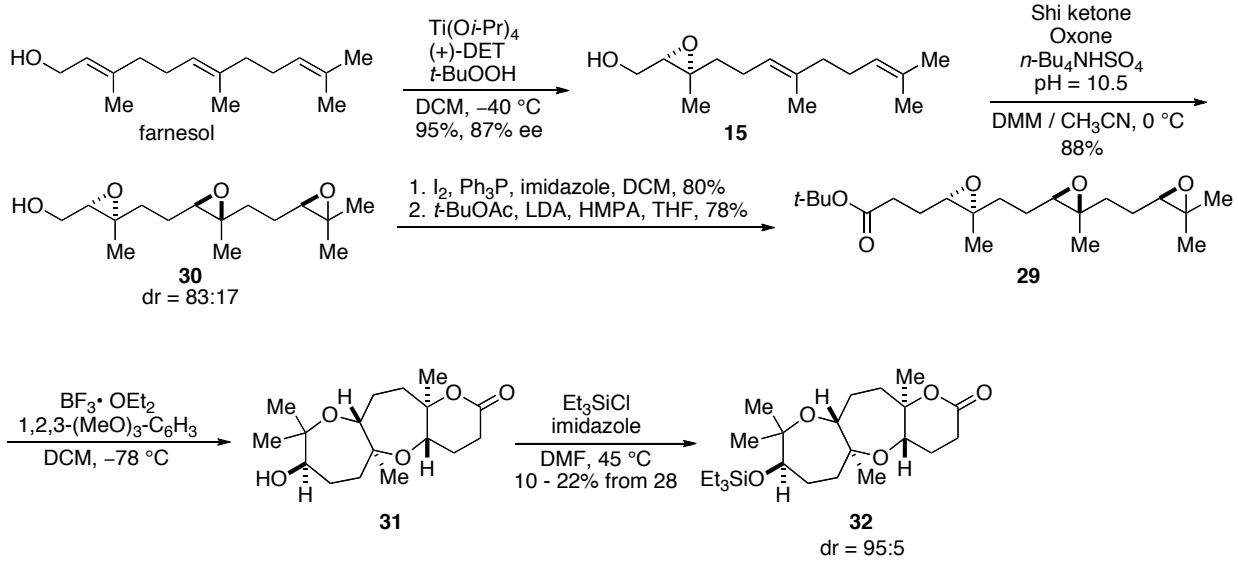
Scheme 19



The triepoxide *tert*-butyl ester (**29**) was prepared in four steps from farnesol (Scheme 20). Sharpless asymmetric epoxidation followed by a Shi asymmetric epoxidation provide triepoxide allylic alcohol **30** as a mixture of diastereomers (dr ~ 83:17). Conversion of the alcohol to an iodide and displacement of the iodide with an enolate derived from *tert*-butyl acetate provided tripoxide *tert*-butyl ester **29**.

The triepoxide *tert*-butyl ester was treated with $BF_3 \cdot OEt_2$ to induce the epoxide-opening cascade (Scheme 20). A mixture of products was observed, but the major cyclization product was the desired fused tricyclic ether **31**. Further purification with chlorotriethylsilane allowed isolation of **32** with dr > 95:5. The structure of **31** was confirmed by X-ray crystallography (Figure 4). Hence, using an epoxide-opening cascade the tricyclic ether system of *ent*-**1** was obtained in six steps from farnesol.

Scheme 20



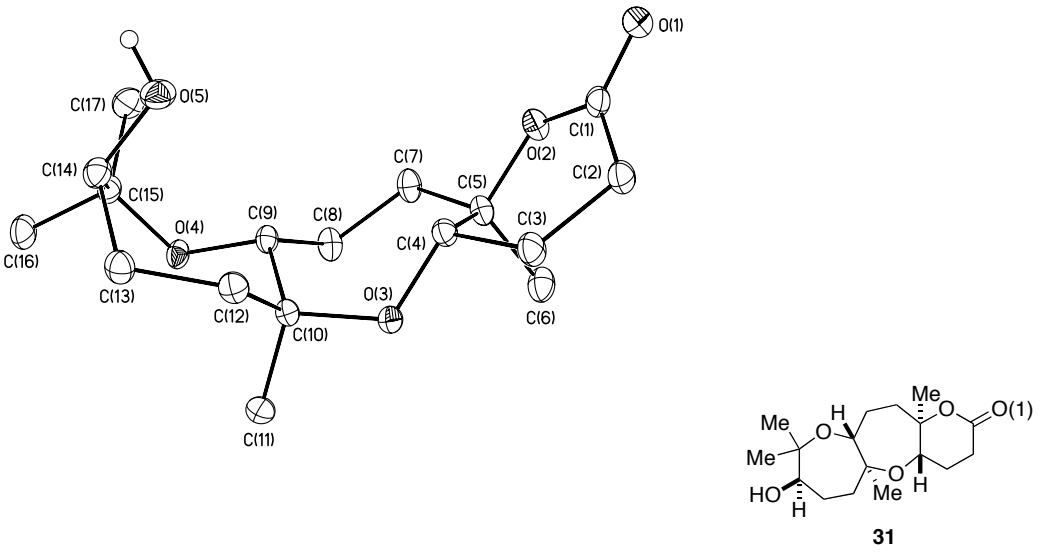


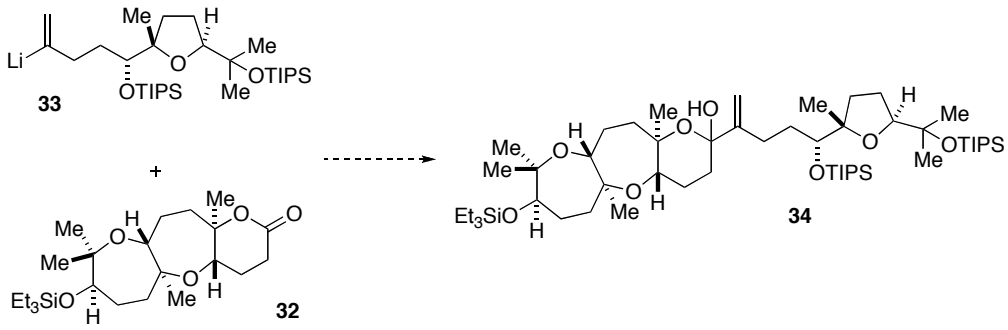
Figure 4. ORTEP drawing of **31**. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted (except O–H) for clarity.

Coupling of the Tricyclic Ether Fragment and the Tetrahydrofuran Fragment

Diastereoselective Formation of the Allylic Ether Stereocenter

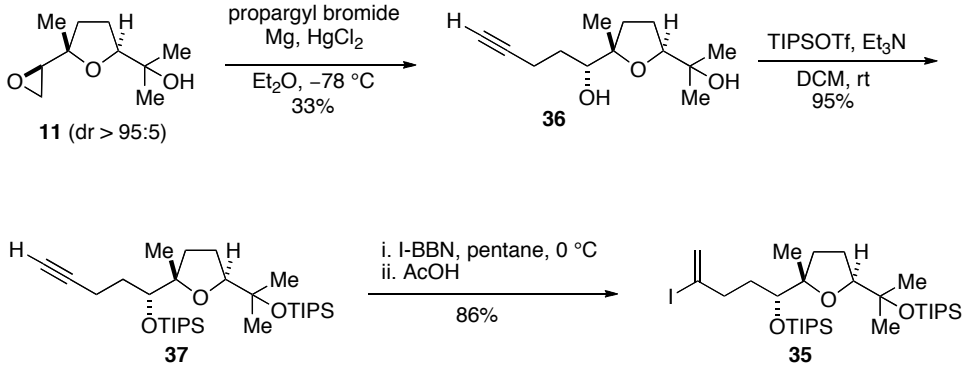
With tricyclic ether fragment of *ent*-**1** easily obtained in gram quantities, the nucleophilic addition of alkenyllithium **33** to lactone **32** was investigated (Scheme 21). The resulting lactol would then be reduced through an oxocarbenium intermediate.

Scheme 21



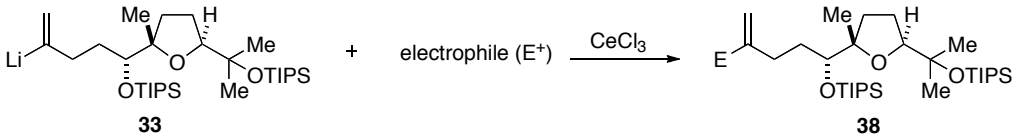
Alkenyl iodide **35** was prepared from epoxy furan **11** (Scheme 22). Addition of allenyl magnesium bromide to epoxy furan **11**[23] followed by TIPS protection afforded alkyne **37** and the allenyl product, which were separated by column chromatography. Iodoboration of alkyne **37** with acetic acid workup isolated alkenyl iodide **35**.[24]

Scheme 22

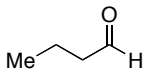
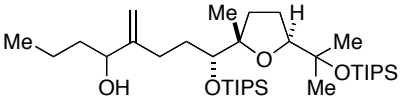
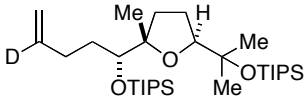
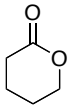
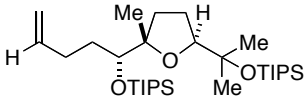
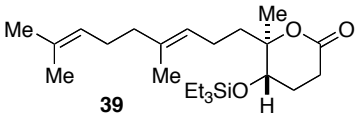
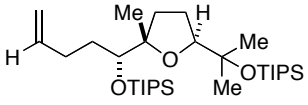
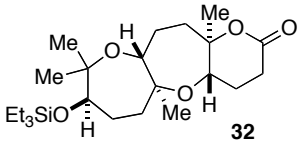
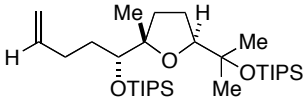


Lithium halogen exchange of iodide **35** with *tert*-butyl lithium generated alkenyl lithium **33** in situ, which was able to add to *n*-butyraldehyde in the presence of $CeCl_3$ to give an allylic alcohol **38a** (Table 2, entry 1). Quenching alkenyl lithium **33** with D_2O provided the deuterated alkene **38b** (entry 2). The same alkenyl lithium (in the presence of $CeCl_3$) cannot add to any lactone, including valerolactone, lactone **39** and lactone **32**. It appeared that the alkenyl cerium was not nucleophilic enough to add to any lactone. Only the protonated product **38c** was observed after aqueous workup (entries 3-5).

Table 2. Addition of Alkenyl Lithium **33** to Various Electrophiles



33 **38**

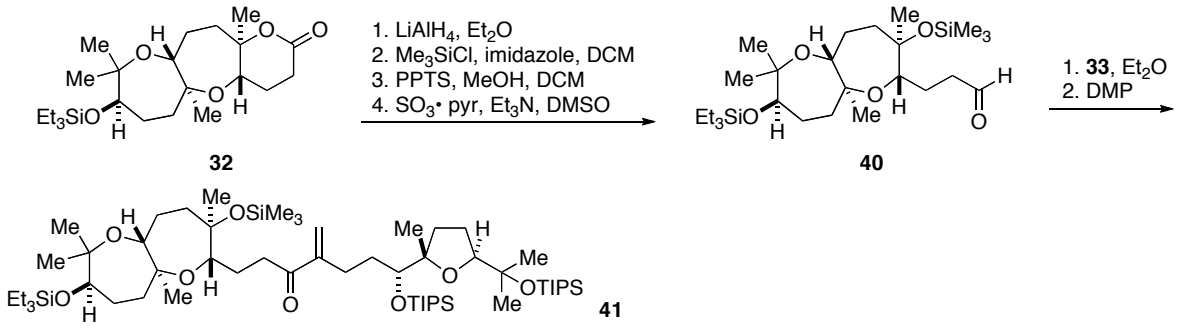
entry	electrophile (E^+)	**38**
1		 **38a**
2[a]	D_2O	 **38b**
3	i.  ii. D_2O	 **38c**
4	 **39**	 **38c**
5	 **32**	 **38c**

[a] No $CeCl_3$ was added.

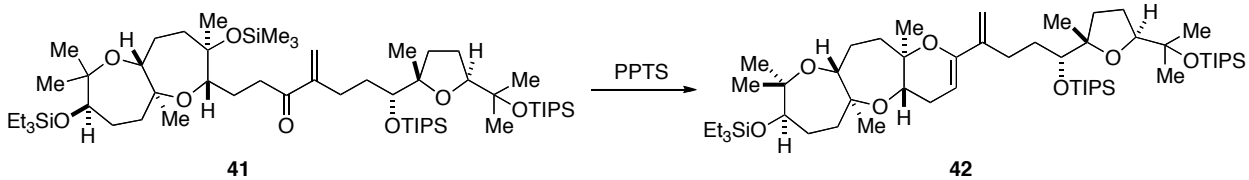
Inspecting the crystal structure of **32** revealed that the lactone was very hindered (Figure 4). One side of the lactone carbonyl was in the concave face of the tricyclic ether structure, while the other side of the lactone carbonyl was blocked by an axial methyl group. The presence of a triethyl silyl group on lactone **32** further increased the steric congestion of the concave face of the tricyclic ether.

To avoid the hindered cyclic ether system, lactone **32** was opened by $LiAlH_4$ reduction to a diol (Scheme 23). Protecting group manipulation followed by a Parikh-Doering oxidation of the primary alcohol provided aldehyde **40**. Addition of alkenyl lithium **33** to the aldehyde provided an allylic alcohol. Oxidation of the allylic alcohol to an enone, and removal of trimethyl silyl group yielded alcohol **41**. Treatment of this alcohol with mild acid provided enol ether **42**, instead of the desired lactol (Scheme 24). Attempt to reduce the enol ether using sodium cyanoborohydride in the presence of acetic acid resulted in recovery of **42**.

Scheme 23



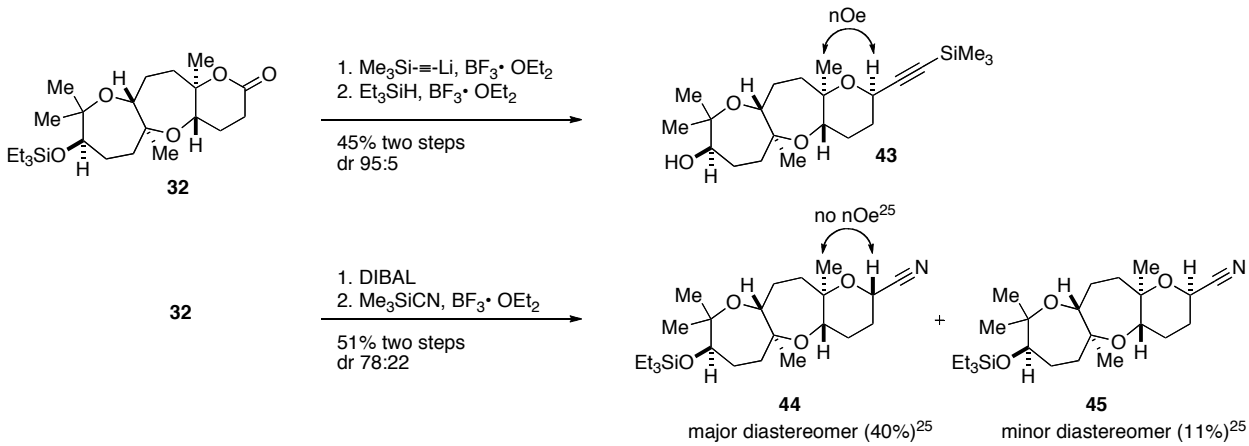
Scheme 24



Nucleophilic addition reactions with lactone **32** were re-evaluated with a less basic and more nucleophilic species such as lithium TMS-acetylide (Scheme 25). In the presence of BF_3•OEt_2, lithium TMS-acetylide added to lactone **32** to form a lactol, which was prone to elimination. After an aqueous workup, the crude reaction mixture was immediately treated with triethylsilane and BF_3•OEt_2 to afford proparylic ether **43**. A NOSEY experiment indicated that the propargylic proton was *syn* to the neighboring methyl group, corresponding to the undesired diastereomer. This result suggested that the concave face of the tricyclic ether ring exerted a stronger steric effect than the axial methyl group in the lactone.

To reverse the diastereoselectivity, lactone **32** was reduced by DIBAL to a hemiacetal (Scheme 25). Addition of TMSCN to the hemiacetal in the presence of BF_3•OEt_2 yielded the desired diastereomer as the major product[25] (**44**), along with the undesired diastereomer[25] (**45**). The selectivity may be due in part to an anomeric effect from the cyano group.[26a] Alternatively, the low diastereoselectivity of the cyanide addition reaction agreed with Woerpel's observation that cyanide addition was less selective than addition of other nucleophiles such as allylsilane, possibly because cyanide addition is much faster.[26b]

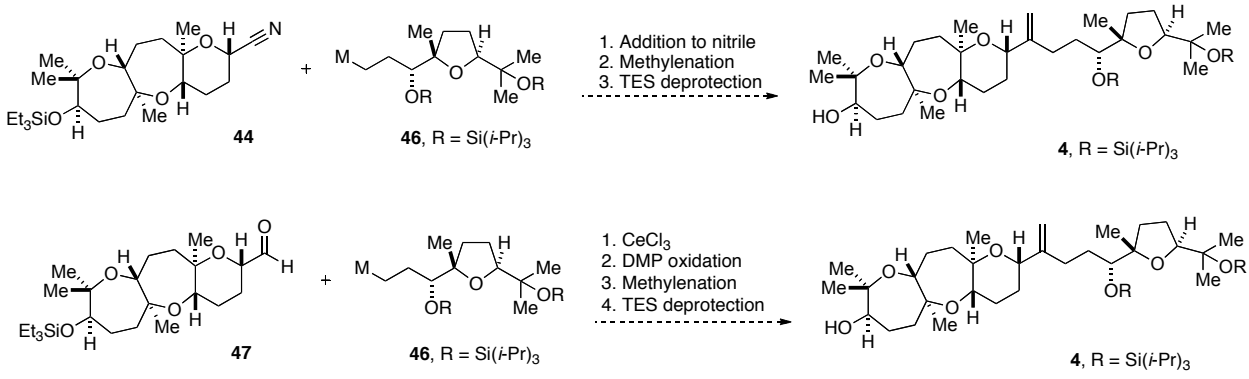
Scheme 25



*Functionalization of Nitriles **44** and **45***

Two classical transformations were envisioned for the installation of the furan side chain to nitrile **44** (Scheme 26). Alkyl metal **46** could either add directly to nitrile **44** to form a ketone, that could be converted to an exo-methylene group to give **4** after removal of the TES group. Alternatively, nitrile **44** could be reduced to aldehyde **47**. Addition of alkyl metal **46** to this aldehyde, oxidation of the resulting alcohol, and methylenation of the ketone would also provide **4** after removal of the TES group.

Scheme 26

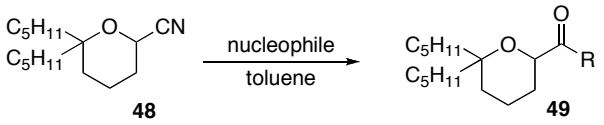


44 **46**, R = Si(*i*-Pr)$_3$ **4**, R = Si(*i*-Pr)$_3$

47 **46**, R = Si(*i*-Pr)$_3$ **4**, R = Si(*i*-Pr)$_3$

The nucleophilic addition of an alkyl metal to a nitrile was first studied on **48**, which possesses a similar substitution pattern to nitrile **44** (Table 3). Methylmagnesium bromide added to nitrile **48** to provide methyl ketone **49a** in good yield (entry 1). Addition of Ni(acac)$_2$ improved the yield of the methyl Grignard addition (entry 2). Dimethylzinc also added to nitrile **48** in the presence of Ni(acac)$_2$ in a similar yield as the addition of methyl Grignard alone (entry 3). Other alkyl nucleophiles such as pentylmagnesium bromide and even butyl lithium added to nitrile **48** to give ketone **49b** and **49c** respectively (entries 4-5).

Table 3. Nucleophilic Addition Reactions to Nitrile **48**

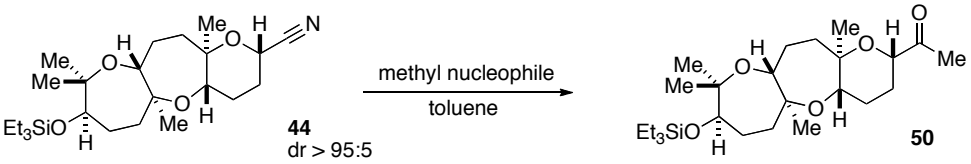


48 **49**

entry	nucleophile	temperature	yield (%)	R	
1	MeMgBr	–10 °C to rt	70	Me	(**49a**)
2	MeMgBr, $Ni(acac)_2$	rt	95	Me	(**49a**)
3	Me_2Zn, $Ni(acac)_2$	rt	76	Me	(**49a**)
4	*n*-$C_5H_{11}MgBr$, $Ni(acac)_2$	rt	74	*n*-C_5H_{11}	(**49b**)
5	*n*-BuLi	–5 °C to rt	60	*n*-Bu	(**49c**)

Nitrile **44** (dr > 95:5) displayed very different reactivity (Table 4). No methyl ketone **50** was observed when methylmagensium bromide was added alone (entry 1). A mixture of methylmagnesium bromide and $Ni(acac)_2$ allowed the addition to proceed and provided methyl ketone **50** in 50% yield with a slight erosion of diastereomeric ratio (93:7) after only 30 min (entry 2). Increasing the reaction time further eroded the diastereomeric ratio but increased the yield of methyl ketone (entries 3-4). Nitrile **44** was not very reactive to Me_2Zn / $Ni(acac)_2$, but no epimerization was observed after one hour (entry 5). Finally, slow addition of methylmagnesium bromide to a mixture of nitrile **44** and $Ni(acac)_2$ completely suppressed epimerization (entry 6). On the other hand, addition of various methyl nucleophiles such as methylmagnesium bromide, trimethylaluminum, and dimethylzinc to nitrile **45** (dr > 95:5) in the presence of $Ni(acac)_2$ all provided methyl ketone **53** with only one diastereomer observed after 18 h at room temperature (Table 5).

Table 4. Methyl Nucleophile Addition Reactions to Nitrile **44**



44
dr > 95:5

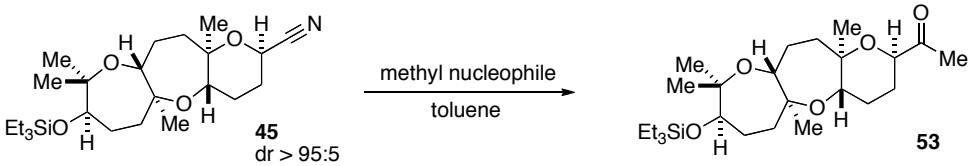
methyl nucleophile
toluene

50

entry[a]	methyl nucleophile	temperature	time	yield (%)	dr[b]
1	MeMgBr	−15 °C to −8 °C	30 min	<1%	--
2	MeMgBr, $Ni(acac)_2$	−15 °C to −8 °C	30 min	50	93:7
3	MeMgBr, $Ni(acac)_2$	4 °C	1h	50	84:16
4	MeMgBr, $Ni(acac)_2$	4 °C to rt	6h	70	50:50
5	Me_2Zn, $Ni(acac)_2$	−15 °C	1h	30[c]	>95:5
6[d]	MeMgBr, $Ni(acac)_2$	−15 °C	1h	50	>95:5

[a] General procedure: Methyl nucleophile as described in the entry was dissolved in toluene. The reaction was cooled to the specified temperature. Nitrile **44** was added. The reaction was stirred for a specified time and warmed to the specified temperature. The reaction was quenched with 0.5M HCl. [b] Determined by ^1H NMR. [c] Yield was based on recovered nitrile. [d] MeMgBr was added to a mixture of nitrile and $Ni(acac)_2$ over 5 min.

Table 5. Methyl Nucleophile Addition Reactions to Nitrile **45**



45
dr > 95:5

methyl nucleophile
toluene

53

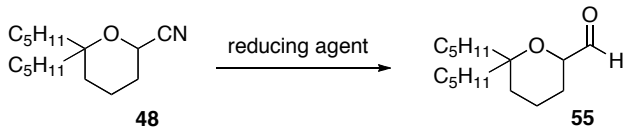
entry[a]	methyl nucleophile	temperature	time	yield (%)	dr[b]
1	MeMgBr, $Ni(acac)_2$	rt	18h	58	>95:5
2	Me_3Al, $Ni(acac)_2$	rt	18h	46	>95:5
3	Me_2Zn, $Ni(acac)_2$	rt	18h	83	>95:5

[a] General procedure: Methyl nucleophile as described in the entry was dissolved in toluene. The reaction was cooled to the specified temperature. Nitrile **45** was added. The reaction was stirred for a specified time and warmed to the specified temperature. The reaction was quenched with 0.5M HCl. [b] Determined by ^1H NMR.

Unfortunately, methyl-derived organometal reagents were the only alkyl nucleophiles that reacted with nitrile **44**. Attempts to add *n*-pentylmagnesium bromide to a similar nitrile failed to provide the corresponding ketone.[27]

Converting nitrile **44** to aldehyde **47** should enhance its reactivity. Again, the reduction step was optimized first with simple nitrile **48**. It was found that DIBAL was not a good reducing agent for this process (Table 6). Increasing the amount of DIBAL from 100 mol% to 200 mol% slightly increase the yield of aldehyde **55** but dramatically reduced the amount of recovered nitrile (entries 1-3). Further increase of the amount of DIBAL to 250 mol% and 300 mol% lowered the yield of aldehyde **55**, and the recovery of the nitrile was less than 5% (entries 4-5). These observations seemed to be consistent with over-reduction of nitrile **48** by DIBAL. Use of bulkier reducing agents such as Schwartz's reagent cleanly reduced nitrile **48** to aldehyde **55** with significantly improved yield (entry 6).

Table 6. Nitrile Reduction to Aldehyde **55**

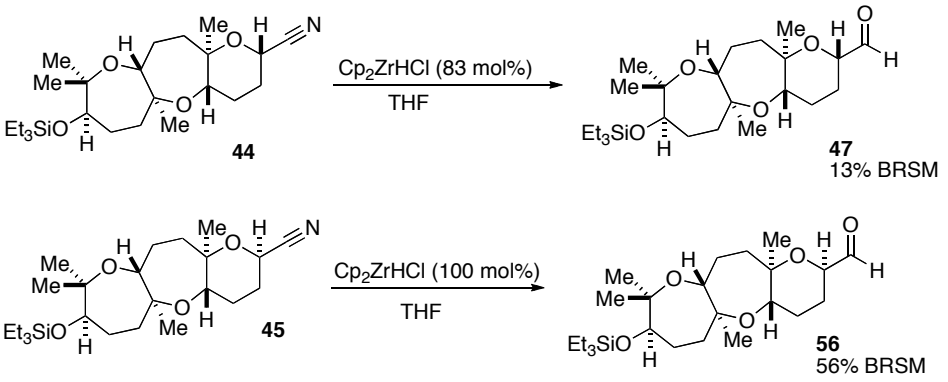


48 **55**

entry	reducing agent	temperature	yield (%)	remaining **48** (%)
1	DIBAL (100 mol%)	−15 °C	12	32
2	DIBAL (150 mol%)	−15 °C	19	10
3	DIBAL (200 mol%)	−15 °C	20	<5
4	DIBAL (250 mol%)	−15 °C	2	<5
5	DIBAL (300 mol%)	−15 °C	2	<5
6	Cp_2ZrHCl (100 mol%)	rt	80	0

However, reduction of nitrile **44** was not efficient even with Schwartz's reagent (Scheme 27). Only 13% yield (BRSM) of aldehyde **47** could be obtained, as compared to 6% yield with DIBAL (no recovered starting material). Reduction of the diasteromeric nitrile **45** with Schwartz's reagent provided better yield of aldehyde **56**. Since aldehyde **47** was difficult to obtain in reasonable quantity, this route was not pursued further.

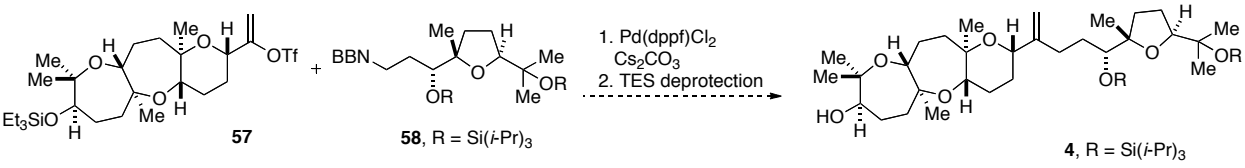
Scheme 27



*Suzuki Coupling of Alkenyl Triflate **57** and B-Alkyl **58***

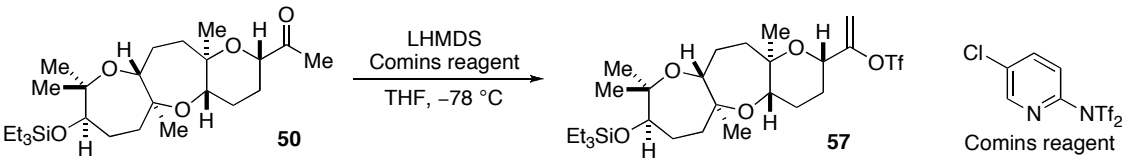
Taking advantage of the methyl ketone (**50**) that can be obtained from nitrile **44**, conversion of methyl ketone **50** to an alkenyl triflate **57** would allow a Suzuki cross coupling with alkyl boron **58** (Scheme 28).[28]

Scheme 28



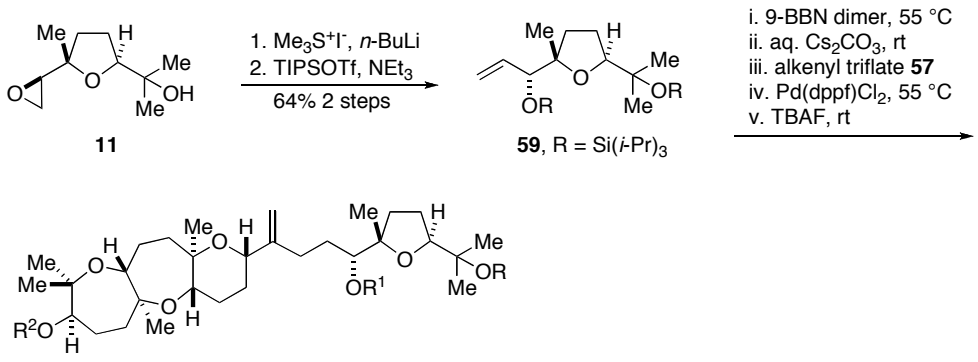
When methyl ketone **50** was added to a mixture of LHMDS and Comins reagent at –78 ºC, alkenyl triflate **57** was formed cleanly (Scheme 29). After an aqueous workup the crude could be used directly in the Suzuki coupling. If methyl ketone **50** was deprotonated with LHMDS before the addition the Comins reagent, a complex mixture of products was formed.

Scheme 29



The boron alkyl reagent (**58**) was prepared from epoxy furan **11** (Scheme 30). Addition of trimethylsulfonium ylide to epoxy furan **11** followed by elimination provided allylic alcohol **59**.[29] After protection of both alcohols as TIPS ethers, hydroboration using 9-BBN dimer afforded boron alkyl reagent **58**. Addition of aqueous Cs_2CO_3 destroyed excess 9-BBN and provided a base for the Suzuki coupling. Addition of the crude alkenyl triflate (**57**) and Pd(dppf)Cl_2 and heating for 18 h yielded the desired cross coupling product in approximately 50% yield. Treatment of the coupling product with TBAF removed the TES group to give alcohol **4** in 26% yield (from **50**). Deprotection of the 2º TIPS group was also observed to give diol **60** in 20% yield (from **50**).

Scheme 30



11 **59**, R = Si(*i*-Pr)$_3$

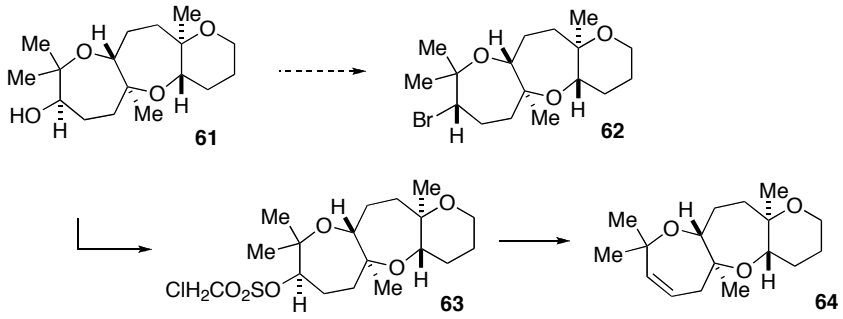
4: R = Si(*i*-Pr)$_3$; R^1 = Si(*i*-Pr)$_3$; R^2 = H, 26%
60: R = Si(*i*-Pr)$_3$; R^1 = H; R^2 = H, 20%

Installation of a Bromine Atom to the Terminal Oxepane

Alcohol **4** contains all the carbons and ether rings in *ent*-**1**. The last transformation required in order to obtain *ent*-**1** is to convert alcohol **4** to a bromide. Alcohol **61** was used to investigate conditions for the preparation of bromide **62** (Scheme 31). Activation of the alcohol as a chloromesylate **63** followed by addition of LiBr resulted in elimination to alkene **64**. The facile elimination can be explained by the β-hydrogen that is *anti* peri-planar to the chloromesylate,

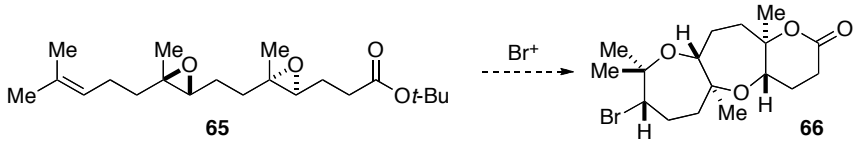
based on the X-ray crystal structure of lactone **32** (Figure 4). Hydrobromination of alkene **64** with HBr led to decomposition of the cyclic ether.

Scheme 31



An alternative route to install the bromide at the terminal oxepane of *ent*-**1** is being pursued. It is common to install a hindered bromide with substitution pattern similar to *ent*-**1** through a bromonium cyclization reaction.[30] Hence, a bromonium-initiated epoxide-opening cascade from diepoxide *tert*-butyl ester **65** might allow a one-step formation of the tricyclic ether system, with the bromide present in the cyclization product (**66**) (Scheme 32).

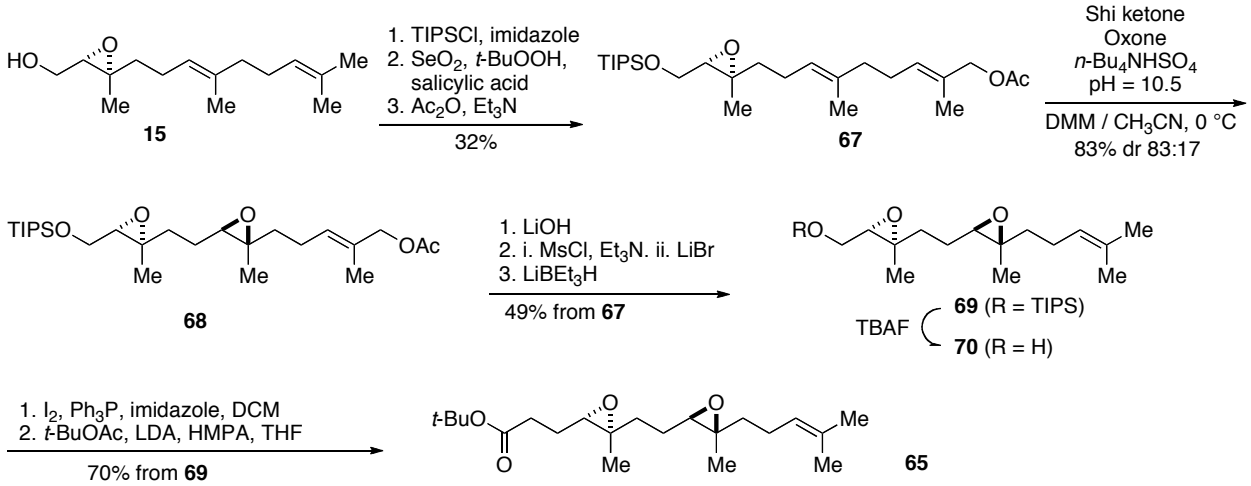
Scheme 32



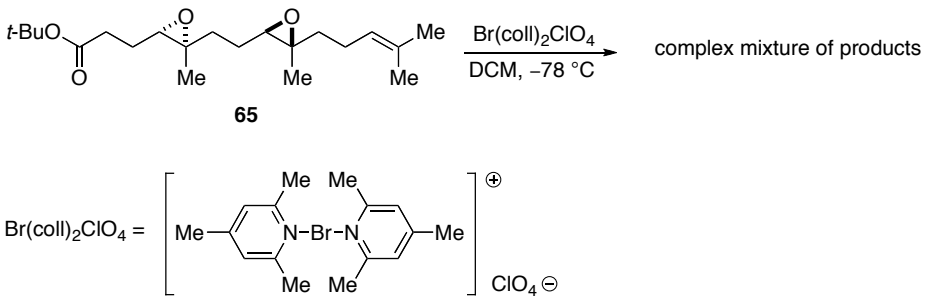
Diepoxide **65** was prepared in a similar fashion as triepoxide **29**. Alcohol **15** was protected as a TIPS ether. Allylic oxidation at the terminal alkene and subsequent conversion to allylic acetate **67** served to protect the terminal alkene from epoxidation in the next step.[31] Shi epoxidation of **67** selectively epoxidized the internal alkene to diepoxide **68**. Conversion of the acetate to a bromide, followed by a reduction by super hydride afforded diepoxide **69**. Silyl group removal, conversion to an iodide, displacement of the iodide with lithium enolate from *tert*-butyl acetate

yielded diepoxide *tert*-butyl ester **65** for bromonium-initiated cascade (Scheme 34). Activation of **65** with $Br(coll)_2ClO_4$[30a-30e] resulted in a complex mixture of products that could not be separated cleanly. An authentic sample of the desired cyclization product is needed to conclude whether bromide **66** was formed during this cascade.

Scheme 33



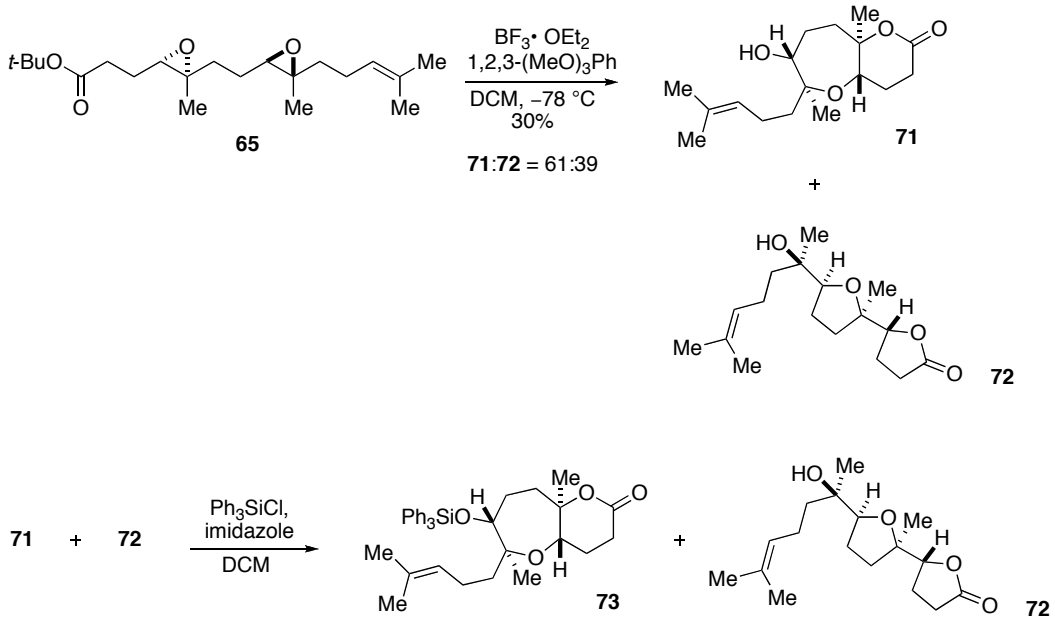
Scheme 34



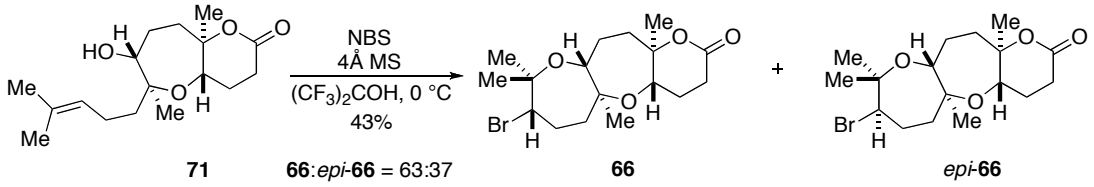
To prepare bromide **66** from a different route, diepoxide **65** was treated with $BF_3{\bullet}OEt_2$ to induce an epoxide-opening cascade to afford two major cyclization products **71** and **72** (Scheme 35).[32] These two products were separated by treatment with chlorotriphenylsilane, which selectively reacted with **71** to silylether **73**.[33] The configurations of **71** and **73** were confirmed by NOSEY experiments. Bromonium-initiated cyclization of **71** by NBS in 1,1,1,3,3,3-

hexafluoropropan-2-ol installed the bromine atom to the tricyclic ether (Scheme 36). The bromooxepane was obtained as a 63:37 mixture of diastereomers (**66** and epi-**66**). A NOSEY experiment of this mixture confirmed that the major diastereomer was **66**. Hence we now have a potential solution for the installation of the hindered bromide in *ent*-**1**.

Scheme 35



Scheme 36



Conclusion

Synthesis of the fused six-seven-seven cyclic ether in *ent*-**1** through an epoxide-opening cascade strategy was explored. Formation of the strained tetrahydropyran ring in *ent*-**1** directly from an epoxide-opening cascade of triepoxide allylic alcohol proved to be difficult. Alternatively, a δ-lactone was obtained using an epoxide-opening cascade of triepoxide *tert*-

butyl ester. The furan side chain was installed via a Suzuki coupling. Conversion of hindered alcohol to a bromide proved to be difficult. Alternatively, a bromonium cyclization allowed the formation of the desired bromo-oxepane.

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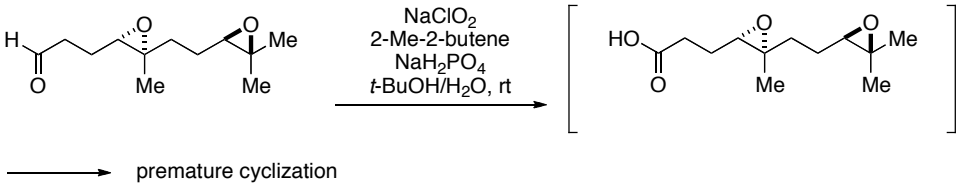
21) Triepoxide allylic alcohol was prepared from a nickel-catalyzed allene–aldehyde reductive coupling.

22) Pinnick oxidation of an epoxy aldehyde with one less epoxide unit resulted in premature cycliczation. Therefore it was assumed that a Pinnick oxidation of triepoxide aldehyde **27** would cyclize even more readily.



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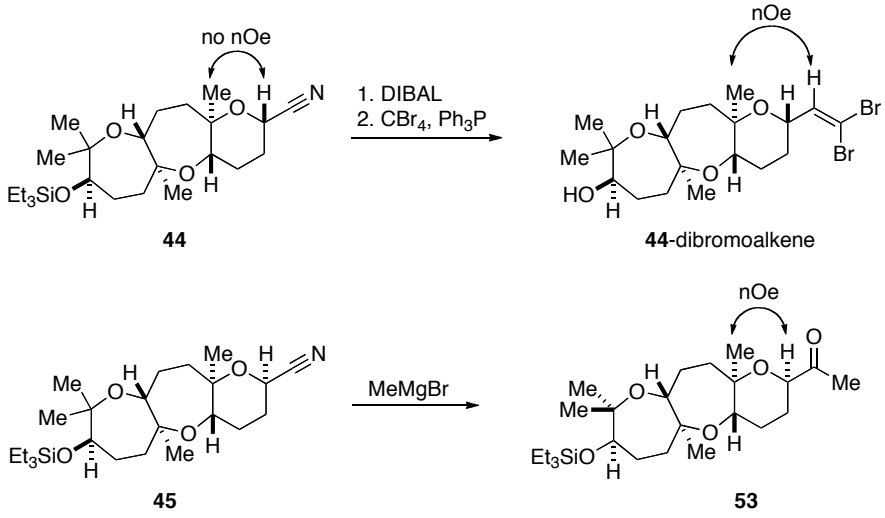
25) To establish the stereochemistry of **44** and **45**, a series of NOSEY experiments were carried out. NOSEY of **44** indicated no nOe interaction between the methyl hydrogens and the cyanohydrin hydrogen on the THP ring. Nitrile **44** was converted to **44**-dibromoalkene. NOSEY of **44**-dibromoalkene indicated nOe interaction between the methyl hydrogens on the THP and the alkenyl hydrogen, confirming that the methyl group and the cyanohydrin hydrogen on the THP of **44** were anti to each other.
The methyl hydrogens and the cyanohydrin hydrogen on nitrile **45** overlapped in the ^{1}H NMR spectrum. Conversion of **45** to **53** and a NOSEY experiment on **53** indicated nOe interaction between the methyl hydrogens on the THP and the α-hydroxy ketone hydrogen. This is consistent with the stereochemical assignment of **45**.



44 **44**-dibromoalkene **45** **53**

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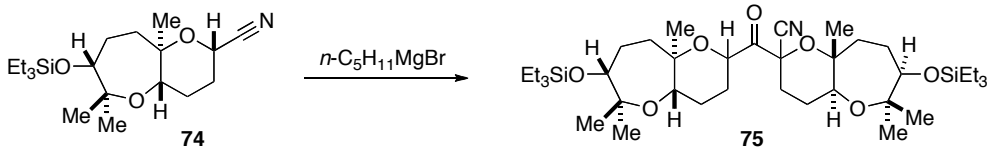
27) Addition nitrile **74** to a mixture of *n*-$C_5H_{11}MgBr$ and $Ni(acac)_2$ yielded cyano-ketone **75**.



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32) The other two possible cyclization products were also observed in small quantity.

33) Alternatively, chlorotriethylsilane was also used (Et_3SiCl, imidazole, DMF / DCM, 45 ºC), which provided better selectivity for **71**.

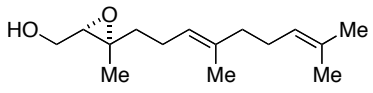
Experimental Section

General Information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran and diethylether were distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane and toluene were distilled over calcium hydride. All other chemicals were used without purification, unless otherwise noted.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz, Bruker 400 MHz, or Bruker 600 MHz spectrometer in $CDCl_3$ or C_6D_6, unless otherwise noted. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) or C_6D_6 (128.39 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H, or AD-H columns. Specific Rotations ($[\alpha]^{20}_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

Synthesis of Epoxy-alcohol 7

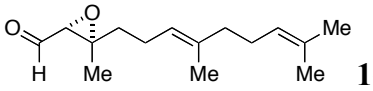


15

L-(+)-Diethyltartrate (428 μL, 2.5 mmol, 12.5 mol%) and 4Å molecular sieves (2g, 0.1g / mmol) were placed in a 50 mL round bottom flask under a stream of argon. DCM (20 mL) was added at room temperature, followed by Ti(O*i*-Pr)$_4$ (600 μL, 2 mmol, 10 mol%). The mixture was stirred vigorously at room temperature for 20 min. *tert*-Butylhydroperoxide (4.54 mL, ~25 mmol, 125 mol%, 5-6 M in decane) was added and the mixture was stirred 5 min at room temperature. The mixture was cooled in a CH_3CN / dry ice bath. The temperature was maintained below –40 °C. Farnesol (5.06 mL, 20 mmol, 100 mol%) was added and stirred in the CH_3CN / dry ice bath for 10 h. The mixture was placed in the freezer overnight.
The next day citric acid monohydrate (420.28 mg, 2 mmol, 10 mol%) was dissolved in 1:1 acetone / diethylether (~ 5 mL) and the solution was added to the reaction mixture. The mixture was stirred vigorously for 20 min at room temperature. Celite was added to the mixture and stirred vigorously for 1 min. The slurry was filtered through a thick pad of celite and the celite was washed with Et_2O. The clear filtrate was washed with saturated $Na_2S_2O_3$ and then dried with $MgSO_4$. Column chromatography isolated 4.53 g of **15** (95% yield). The enantiomeric excess was determined by HPLC of the benzoate to be 87%.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.10 (m, 2H); 3.84 (ddd, *J* = 4.3, 7.5, 12.0 Hz, 1H); 3.70 (ddd, *J* = 4.9, 6.7, 11.8 Hz, 1H); 2.99 (dd, *J* = 4.3, 6.7 Hz, 1H); 2.16-1.94 (m, 6H); 1.71 (m, 1H); 1.69 (s, 3H); 1.614 (s, 3H); 1.608 (s, 3H); 1.48 (m, 1H); 1.32 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 136.0, 131.6, 124.4, 123.3, 63.2, 61.6, 61.4, 39.8, 38.7, 26.8, 25.9, 23.8, 17.9, 17.0, 16.2.
IR (NaCl, thin film): 3422, 2919, 1456, 1384, 1033.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{26}O_2Na$, 261.1825; found, 261.1830.
$[\alpha]^{20}_D$ –4.2 (*c* 1.93, $CHCl_3$)

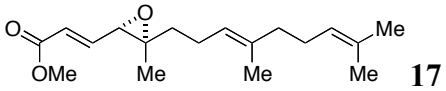
Chiral HPLC analysis: Analysis was performed on the corresponding benzoate (BzCl, Et_3N, DMAP, DCM): (Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.0 mL/min): t_R(2*S*,3*S*) = 7.3 min; t_R(2*R*, 3*R*) = 8.1 min. The enantiomeric excess was determined to be 87%.



16

Alcohol **15** (1.57g, 6.586 mmol, 100 mol%) was dissolved in dichloromethane (50 mL). Triethylamine (4.6 mL, 32.93 mmol, 500 mol%) was added at room temperature. Dimethylsulfoxide (12 mL) was added. The mixture was cooled in an ice/water bath. SO_3•pyridine complex (2.64 g, 16.47 mmol, 250 mol%) was added in one portion. Rinsed the wall of the flask with 5 mL dichloromethane. Stirred in the ice bath for 5 h. Temperature slowly rose to room temperature. The mixture was diluted with diethylether, washed with saturated NH_4Cl and dried with $MgSO_4$. Column chromatography isolated 1.38 g of **16** (88% yield).

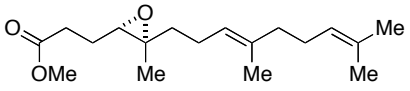
^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.46 (d, *J* = 5.0 Hz, 1H); 5.08 (t, *J* = 7.0 Hz, 2H); 3.20 (d, *J* = 5.0Hz, 1H); 2.20-1.90 (m, 6H); 1.73 (m, 1H); 1.67 (s, 3H); 1.60 (s, 6H); 1.58 (m, 1H); 1.45 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 199.8, 136.6, 131.7, 124.3, 122.6, 64.4, 63.7, 39.8, 38.5, 26.7, 25.9, 23.5, 17.9, 17.4, 16.2.
IR (NaCl, thin film): 2967, 2918, 1723, 1450, 1384.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{24}O_2Na$, 259.1669; found, 259.1673.
$[\alpha]^{20}_D$ +71.5 (*c* 2.0, $CHCl_3$)



17

Aldehyde **16** (1.38 g, 5.839 mmol, 100 mol%) was dissolved in dichloromethane (55 mL) at room temperature. (Methoxycarbonylmethylene)triphenylphosphorane (2.0 g, 11.68 mmol, 200 mol%) was added in one portion. The wall of the flask was rinsed with dichloromethane (5 mL). The mixture was stirred at room temperature overnight. The mixture was loaded directly to a silica column. Column chromatography isolated 1.57 g of **17** and its geometric isomer as a mixture (91% yield).

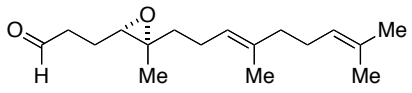
^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.84 (dd, *J* = 6.4, 15.7 Hz, 1H); 6.10 (dd, *J* = 1.0, 15.7 Hz, 1H); 5.08 (m, 2H); 3.75 (s, 3H); 3.33 (dd, *J* = 0.8, 6.4 Hz, 1H); 2.20-1.90 (m, 6H); 1.74 (m, 1H); 1.68 (s, 3H); 1.60 (s, 6H); 1.55 (m, 1H); 1.28 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.3, 143.4, 136.2, 131.7, 124.5, 124.3, 123.2, 64.4, 61.6, 51.9, 39.8, 38.6, 26.8, 25.9, 23.8, 17.9, 16.7, 16.2.
IR (NaCl, thin film): 2966, 2919, 2857, 1726, 1437, 1263, 1171.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{18}H_{28}O_3Na$, 315.1931; found, 315.1927.
$[\alpha]^{20}_D$ +3.5 (*c* 1.7, $CHCl_3$)



18

Enoate **17** (1.210 g, 4.138 mmol, 100 mol%) was placed in a 100 mL round bottom flask. The flask was evacuated under vacuum and back-filled with argon. Tetrahydrofuran (30 mL) was added at room temperature, followed by phenylsilane (0.767 mL, 6.201 mmol, 150 mol%). The mixture was cooled in an ice/water bath. Triphenylphosphine-copper(I)-hydride-hexamer (161 mg, 0.08275 mmol, 2 mol%) was added in one portion. Rinse the wall of the flask with tetrahydrofuran (10 mL). Temperature gradually rose to room temperature. After a total of 2.5 h, TLC indicated that starting material was consumed. Still in the water bath, septum was removed and water (10 mL) was added. Bubbling occurred. The mixture was stirred in the water bath for 30 min. Celite was added while the mixture was vigorously stirring and the solid was filtered and rinsed with diethyl ether (200 mL). The filtrate was washed with saturated NH_4Cl. The organic fraction was dried with $MgSO_4$ and then filtered through a small plug of silica. Column chromatography isolated 1.2 g of ester **18** (98% yield).

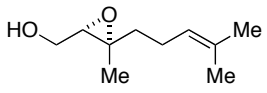
^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.08 (t, J = 6.8 Hz, 2H); 3.67 (s, 3H); 2.76 (dd, J = 5.4, 7.2 Hz, 1H); 2.47 (m, 2H); 2.20-1.60 (m, 9H); 1.67 (s, 3H); 1.59 (s, 6H); 1.42 (m, 1H); 1.27 (s, 3H).
^{1}H NMR (400 MHz, C_6D_6, δ): 5.23 (t, J = 6.7 Hz, 1H); 5.17 (t, J = 7.1 Hz, 1H); 3.31 (s, 3H); 2.62 (dd, J = 5.6, 7.1 Hz, 1H); 2.30-1.97 (m, 8H); 1.73 (m, 2H); 1.68 (s, 3H); 1.57 (s, 3H); 1.55 (s, 3H); 1.41 (m, 1H); 1.09 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 173.5, 135.8, 131.6, 124.4, 123.6, 62.6, 61.3, 51.9, 39.8, 38.9, 31.1, 26.8, 35.9, 24.4, 23.9, 17.9, 16.7, 16.2.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{18}H_{30}O_3Na$, 317.2087; found, 317.2088.
IR (NaCl, thin film): 2925, 1741, 1437, 1384, 1170.
$[\alpha]^{20}_D$ –9.05 (*c* 2.1, $CHCl_3$)



8

Ester **18** (966 mg, 3.281 mmol, 100 mol%) was dissolved in toluene (30 mL). The solution was cooled to –83 °C in a diethylether/dry ice bath. Stirred at –83 °C for 5 min. DIBAL solution (4.3 mL, 4.2652 mmol, 130 mol%, 1 M in toluene) was diluted with toluene (16 mL) and added to the reaction mixture over 45 min. The temperature was kept below –80 °C throughout the reaction. After the addition completed the mixture was stirred below –80 °C for 1 h. Methanol (4 mL) was added, followed by saturated Rochelle's salt solution (30 mL). The cold bath was removed. The mixture was stirred for 1 h after the ice melted. The mixture was diluted with diethylether, washed with water and dried with $MgSO_4$. Column chromatography isolated 823 mg of **8** (94% yield).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.82 (t, *J* = 1.2 Hz, 1H); 5.08 (t, *J* = 5.5 Hz, 2H); 2.74 (dd, *J* = 5.1, 7.6 Hz, 1H); 2.62 (m, 2H); 2.10-1.85 (m, 7H); 1.82-1.60 (m, 2H); 1.67 (s, 3H); 1.60 (s, 3H); 1.59 (s, 3H); 1.43 (m, 1H); 1.27 (s, 3H).
^{1}H NMR (400 MHz, C_6H_6, δ): 9.24 (s, 1H); 5.24 (t, J = 6.8 Hz, 1H); 5.17 (t, J = 6.1 Hz, 1H); 2.49 (dd, J = 5.2, 7.5 Hz, 1H); 2.51-2.48 (m, 8H); 1.68 (s, 3H); 1.64-1.34 (m, 4H); 1.57 (s, 3H); 1.56 (s, 3H); 1.05 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 201.2, 135.8, 131.6, 124.4, 123.6, 62.5, 61.5, 41.0, 39.9, 38.8, 26.8, 25.6, 23.9, 21.6, 17.8, 16.8, 16.2.
^{13}C NMR (100 MHz, C_6D_6, δ): 200.2, 135.8, 131.6, 125.2, 124.6, 62.3, 60.9, 41.2, 40.5, 39.3, 27.5, 26.2, 24.5, 22.1, 18.1, 17.0, 16.4.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{28}O_2Na$, 287.1982; found, 287.1991.
IR (NaCl, thin film): 2966, 2924, 1726, 1451, 1385, 1108.
$[\alpha]^{20}_D$ –10.4 (*c* 3.16, CH_2Cl_2)
$[\alpha]^{20}_D$ –11.4 (*c* 4.23, $CHCl_3$)



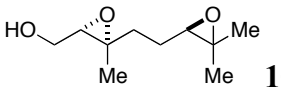
9

L-(+)-Diethyltartrate (5.55 mL, 32.4 mmol, 12.5 mol%) and 4Å molecular sieves (26 g, 0.1 g / mmol alkene) were placed in a 500 mL Erlenmeyer flask under a stream of argon. Dichloromethane (260 mL) was added at room temperature, followed by Ti(O*i*-Pr)$_4$ (7.7 mL, 25.9 mmol, 10 mol%). The mixture was stirred vigorously at room temperature for 20 min. *tert*-Butylhydroperoxide (59 mL, ~324 mmol, 125 mol%, 5-6 M in decane) was added and the mixture was stirred 10 min at room temperature. The mixture was cooled in a CH_3CN / dry ice bath. The temperature was maintained below –40 °C. Geraniol (45.5 mL, 259 mmol, 100 mol%) was added and stirred in the CH_3CN / dry ice bath for 10 h. The mixture was placed in the freezer overnight.
The next day citric acid monohydrate (5.44 g, 25.9 mmol, 10 mol%) was dissolved in 1:1 acetone / diethylether (just enough to dissolve all citric acid monohydrate) and the solution was added to the reaction mixture. The mixture was stirred vigorously for 1 h at room temperature. Celite was added to the mixture and stirred vigorously for 1 min. The slurry was filtered through a thick pad of celite and the celite was washed with Et_2O. The mixture was concentrated and saturated $Na_2S_2O_3$ (400 mL) was added to the ether solution. White solid precipitated, which was filtered with the aid of celite and silica gel to give a clear solution. Layers were separated. Aqueous layer was extracted again with Et_2O. Combined organic solution was washed again with saturated $Na_2S_2O_3$ and then dried with $MgSO_4$.
The organic solution was concentrated to ~400 mL. Sodium hydroxide solution in brine (32.4 mL, this solution was prepared from 30 g NaOH, 5 g NaCl and 90 mL H_2O) was added and the mixture was stirred vigorously in an ice / water bath for 45 min. The aqueous layer was separated and the organic layer was dried with $MgSO_4$. The organic solution was concentrated and vacuum distillation removed low boiling materials and isolated 42 g of epoxide **29** (95% yield). The crude was used directly.

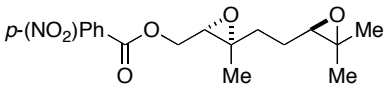
The enantiomeric excess was determined by HPLC of the benzoate to be 84.5%.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.05 (t, *J* = 7.2 Hz, 1H); 3.79 (dd, *J* = 4.1, 12.2 Hz, 1H); 3.64 (dd, *J* = 6.9, 12.2 Hz, 1H); 2.96 (dd, *J* = 4.12, 6.9 Hz, 1H); 2.70 (bs, 1H); 2.06 (m, 2H); 1.66 (s, 3H); 1.64 (m, 1H); 1.58 (s, 3H); 1.44 (m, 1H); 1.27 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ): 132.3, 123.4, 63.4, 61.5, 61.4, 38.6, 25.8, 23.8, 17.8, 16.9.
IR (NaCl, thin film): 3419, 2926, 1452, 1384, 1033.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{10}H_{18}O_2Na$, 193.1199; found, 193.1203.
$[\alpha]^{20}_D$ –4.7 (*c* 10.0, $CHCl_3$)

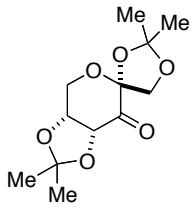
Chiral HPLC analysis: Analysis was performed on the corresponding benzoate of the epoxide alcohol (BzCl, Et_3N, DCM): Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.0 mL/min. The retention times for the two enantiomers were 8.9 and 9.5 min.



10



10-NO_2-benzoate



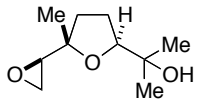
(–)-Shi ketone

Alcohol **9** (5.533 g, 32.5 mmol, 100 mol%), Bu_4NHSO_4 (441 mg, 1.3 mmol, 4 mol%), and (–)-Shi ketone (2.323 g, 9.75 mmol, 30 mol%) were placed in a 2 L bottle with a big stir bar. 0.05 M $Na_2B_4O_7$•$10H_2O$ in $4x10^{-4}$ M EDTA (325 mL, 10 mL / mmol alkene) added, followed by a 1:2 mixture of CH_3CN / DMM (488 mL). This mixture was cooled in an ice / water bath and stirred vigorously. Oxone (27.57 g, 44.85 mmol, 138 mol%) in $4x10^{-4}$ M EDTA (214 mL, to make a 0.21 M oxone solution) and aqueous K_2CO_3 solution (0.89 M, same volume as the oxone solution) were added to the reaction mixture simultaneously over ~30 min. Once the addition completed the reaction mixture was stirred for another 15 min and quenched with water. The mixture was extracted with CH_2Cl_2 (1.5 L), dried with $MgSO_4$, and column chromatography isolated 5.024 g of epoxy-alcohol **10** (83% yield).

To upgrade the enantio- and diastereoratio of epoxy-alcohol **10**, this epoxy-alcohol was converted to a *p*-nitrobenzoate (*p*-NO_2-BzCl, Et_3N, CH_2Cl_2, rt) and recrystallized to afford a pale yellow solid. Saponification of the resulting *p*-nitrobenzoate (1 M NaOH, 1:3 H_2O / THF, rt; Extraction with Et_2O) returned epoxy-alcohol **10** with 95% ee and 95:5 dr.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.77 (dd, *J* = 5.4, 11.7 Hz, 1H); 3.67 (dd, *J* = 6.2, 11.8 Hz, 1H); 2.99 (t, *J* = 5.8 Hz, 1H); 2.74 (dd, *J* = 4.1, 8.1 Hz, 1H); 2.65 (bs, 1H); 1.91 (m, 1H); 1.81 (m, 1H); 1.56 (m, 2H); 1.310 (s, 3H); 1.306 (s, 3H); 1.28 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 64.5, 63.0, 61.0, 60.9, 59.0, 36.3, 25.0, 24.9, 18.9, 16.6.
IR (NaCl, thin film): 3424, 2964, 1458, 1380, 1032.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{10}H_{18}O_3Na$, 209.1148; found, 209.1149.
$[\alpha]^{20}_D$ +35.2 (*c* 1.1, $CHCl_3$) before recrystallization from benzoate.
$[\alpha]^{20}_D$ +39.7 (*c* 3.2, $CHCl_3$) after recrystallization from benzoate.

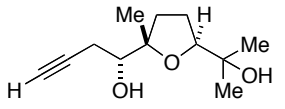
Chiral HPLC analysis: Analysis was performed on the corresponding benzoate of the diepoxide alcohol (BzCl, Et_3N, DMAP, DCM): Chiralcel AD-H, hexanes:2-propanol, 99:1, 1.3 mL/min. The retention times for the four possible diastereomers were 28.6, 30.4, 32.6, and 49.3 min. The retention time of the desired diastereomer was 30.4 min.



11

Epoxyalcohol **10** (2.5132 g, 13.49 mmol, 100 mol%) was dissolved in THF (6 mL) in a 100 mL round bottom flask. The solution was stirred vigorously while NaOH solution (27 mL, 0.5 M, 100 mol%) was added at rt over 2 min. The mixture was stirred 16 h. It was diluted with Et_2O (350 mL) and the layers were separated. The aqueous layer was extracted again with 50 mL Et_2O. The combined organic solution was dried with $MgSO_4$. Column chromatography isolated 1.5 g of epoxide **11** (59% yield).

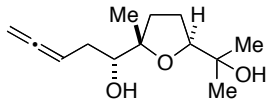
^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.76 (t, *J* = 7.4 Hz, 1H); 3.01 (dd, *J* = 2.8, 4.1 Hz, 1H); 2.72 (t, *J* = 4.8 Hz, 1H); 2.56 (dd, *J* = 2.8, 5.0 Hz, 1H); 2.16 (bs, 1H); 1.82 (m, 3H); 1.60 (m, 1H); 1.25 (s, 3H); 1.20 (s, 3H); 1.11 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 86.9, 81.4, 70.8, 57.2, 44.0, 32.9, 27.6, 26.4, 24.4, 24.3.
IR (NaCl, thin film): 3474, 2976, 2874, 1465, 1373, 1055, 897.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{10}H_{18}O_3Na$, 209.1148; found, 209.1155.
$[\alpha]^{20}_D$ +2.08 (*c* 2.4, $CHCl_3$).



12

Epoxide **11** (1.220 g, 6.550 mmol, 100 mol%, dr 83:17) was placed in a round bottom flask and the flask purged with argon. Lithium acetylide ethylene diamine complex (2.128 g, 19.7 mmol, 300 mol%, previously stored in a glove box) was quickly added to the epoxide. DMSO (13 mL) was added to the mixture. The reaction was exothermic. The mixture was stirred at rt for 18 h. Epoxide **11** was all consumed as judged by GCMS. The reaction mixture was cooled in an ice / water bath and quenched with water. The mixture was acidified to pH ~3 by 1M HCl, extracted with Et_2O, and dried with $MgSO_4$. Column chromatography isolated 810 mg of **12** (58% yield).

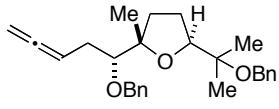
IR (NaCl, thin film): 3420, 3310, 2975, 2120, 1457, 1377, 1075.



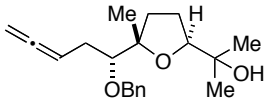
13

CuI (359 mg, 1.884 mmol, 50 mol%), $(CH_2O)_n$ (283 mg, 9.421 mmol, 250 mol%), and *i*-Pr_2NH (1.06 mL, 7.536 mmol, 200 mol%) were placed in a pressure vessel and connected to an Ar line. Alkyne **12** (800 mg, 3.768 mmol, 100 mol%) in minimal Et_2O was added, followed by dioxane (8 mL). Et_2O was removed by bubbling nitrogen through the solution. The pressure vessel was purged with argon, then quickly sealed with a screw cap. The mixture was heated to 100 ˚C for 14 h. The mixture was cooled to rt. Solid was removed by filtration over celite and washed with Et_2O. Solvent was removed and redissolved in Et_2O and water was added. The mixture was acidified with 1 M HCl. Layers were separated and the aqueous layer was extracted again with Et_2O. The organic solution was washed with saturated $NaHCO_3$ and dried with $MgSO_4$. Column chromatography allowed separation of any minor diastereomer (hexane/ethyl acetate) to yield 542 mg of allene **13** (63% yield).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.23 (quintet, *J* = 6.9 Hz, 1H); 4.73 (m, 2H); 3.78 (dd, *J* = 6.0, 10.0 Hz, 1H); 3.63 (dt, *J* = 2.4, 4.8 Hz, 1H); 2.23 (s, 1H); 2.27 (m, 1H); 2.19-2.00 (m, 2H); 2.07 (s, 1H); 1.95-1.81 (m, 2H); 1.62 m, 1H); 1.23 (s, 3H); 1.18 (s, 3H); 1.14 (s, 3H).
IR (NaCl, thin film): 3435, 2974, 1956, 1375, 1082, 843.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_{22}O_3Na$, 249.1461; found, 249.1459.



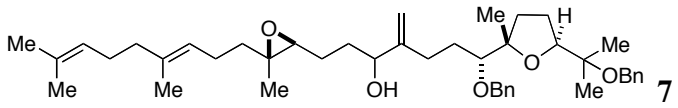
6



monobenzylether

Allene **13** (390 mg, 1.723 mmol, 100 mol%) was dissolved in THF (6.4 mL). Sodium hydride (92 mg, 3.844 mmol, 223 mol%) was added and the reaction was stirred at rt for 2 min. Benzyl bromide (0.457 mL, 3.844 mmol, 223 mol%) and *n*-BuNI (473 mg, 1.281 mmol, 74 mol%) were added. The reaction was stirred at rt for 1 h and then 75 ˚C for 18 h. After the reaction mixture was cooled down to rt, it was poured into ice-cold water. This mixture was extracted with Et_2O and dried with $MgSO_4$. Column chromatography isolated 142 mg of monobenzylether (27% yield) and 446 mg of dibenzylether **6** (66% yield). (SN061379)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40-7.10 (m, 10H); 5.22 (quintet, *J* = 7.2 Hz, 1H); 4.73 (dd, *J* = 11.6, 37.2 Hz, 2H); 4.66 (dd, *J* = 2.8, 6.4 Hz, 2H); 4.56 (t, *J* = 2.4 Hz, 2H); 3.98 (dd, *J* = 6.0, 9.6 Hz, 1H); 3.48 (dd, *J* = 3.2, 8.8 Hz, 1H); 2.33 (m, 1H); 2.15 (m, 2H); 1.87 (m, 2H); 1.60 (m, 1H); 1.27 (s, 3H); 1.23 (s, 3H); 1.19 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 209.3, 140.4, 139.5, 128.44, 128.35, 127.9, 127.5, 127.2, 127.1, 88.0, 86.23, 86.15, 85.0, 76.6, 74.8, 74.5, 64.5, 33.4, 31.4, 27.6, 24.3, 22.5, 22.0.



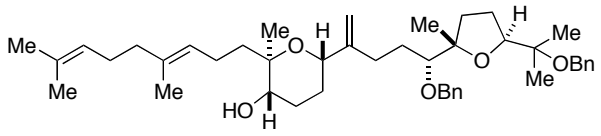
7

$Ni(cod)_2$ (309 mg, 1.1238 mmol, 100 mol%) and Cyp_3P (315 μL, 1.1238 mmol, 100 mol%) was placed into a flask in a glove box. The flask was sealed with a rubber septum and brought out of the glove box. Under argon, aldehyde **8** (594 mg, 2.2477 mmol, 200 mol%) in THF (31 mL) was added to the catalyst mixture at room temperature to yield an orange-yellow solution. TBSH (269 μL, 1.6857 mmol, 150 mol%) was added to the mixture. Allene **6** (440 mg, 1.1238 mmol, 100 mol%) in THF (20 mL) was added to the reaction mixture over 3 h. After addition completed, the reaction mixture was stirred for 15 min. Volatiles were removed by rotavap. The crude was dissolved in Et_2O, washed with sat. NH_4Cl, and dried with $MgSO_4$. Column chromatography isolated an allylic ether in 67% yield. The silyl group was removed by TBAF in THF to yield epoxy-alcohol **7**.

^{1}H NMR (400 MHz, C_6D_6, δ): 7.42 (d, *J* = 7.8 Hz, 2H); 7.39 (d, *J* = 7.2 Hz, 2H); 7.23 (t, *J* = 7.4 Hz, 4H); 7.12 (t, *J* = 7.4 Hz, 2H); 5.21 (m, 2H); 5.14 (s, 0.5H); 5.10 (s, 0.5H); 4.88 (t, *J* = 11.3 Hz, 2H); 4.64 (s, 0.5H); 4.61 (s, 0.5H); 4.50 (dd, *J* = 11.9, 17.8 Hz, 2H); 4.08 (m, 0.5H); 4.00 (m, 0.5H); 3.96 (dd, *J* = 5.6, 9.6 Hz, 1.5H); 3.41 (d, *J* = 8.5 Hz, 1H); 2.67 (m, 1H); 2.35-1.38 (m, 20H); 1.68 (s, 3H); 1.57 (s, 6H); 1.25-1.12 (m, 12H).
^{13}C NMR (100 MHz, C_6D_6, δ): 152.8, 152.7, 141.2, 140.43, 140.41, 135.7, 131.6, 128.9, 128.8, 128.3, 128.2, 127.9, 127.6, 127.5, 125.2, 124.7, 109.9, 87.04, 87.00, 86.96, 85.5, 85.4, 76.6, 75.4, 75.2, 75.0, 74.8, 64.9, 63.7, 63.5, 61.1, 60.9, 40.5, 39.6, 39.5, 33.9, 33.7, 33.4, 33.3, 30.94, 30.90, 29.6, 29.4, 27.8, 27.5, 26.3, 25.9, 25.8, 24.8, 24.7, 24.55, 24.53, 23.0, 22.1, 22.0, 18.1, 17.19, 17.16, 16.4.

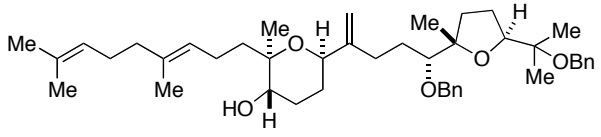
Screening of Epoxide-Opening Reactions by Epoxy-Alcohol 7

Epoxy-alcohol **7** (dr 50:50) was subjected to a variety of Lewis acids and protic acids. A mixture of THPs, (*S*)-**20** and (*R*)-**20**, and THFs, (*S*)-**21** and (*R*)-**21** were observed. Both THPs (*S*)-**20** and (*R*)-**20** were separable by column chromatography (Et_2O / C_6H_6). The two THFs, (*S*)-**21** and (*R*)-**21**, were not separable by column chromatography. Also, Both THPs reacted with *p*-nitrobenzoyl chloride but not the two THFs.



(*S*)-**20**

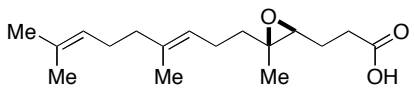
^{1}H NMR (500 MHz, C_6D_6, δ): 7.46 (d, *J* = 7.0 Hz, 2H); 7.40 (d, *J* = 7.4 Hz, 2H); 7.23 (m, 4H); 7.12 (t, *J* = 7.0 Hz, 2H); 5.25 (m, 2H); 5.18 (s, 1H); 4.93 (s, 1H); 4.90 (d, *J* = 11.8 Hz, 1H); 4.67 (d, *J* = 11.6 Hz, 1H); 4.51 (q, *J* = 11.9 Hz, 1H); 3.98 (dd, *J* = 5.8, 9.9 Hz, 1H); 3.94 (d, *J* = 8.4 Hz, 1H); 3.43 (dd, *J* = 2.8, 9.2 Hz, 1H); 3.18 (s, 1H); 2.55 (m, 1H); 2.35-1.40 (m, 19H); 1.69 (s, 3H); 1.61 (s, 3H); 1.58 (s, 3H); 1.25 (s, 3H); 1.23 (s, 3H); 1.21 (s, 3H); 1.20 (s, 3H).
^{13}C NMR (125 MHz, C_6D_6, δ): 151.3, 141.3, 140.6, 135.5, 131.7, 128.9, 128.8, 127.8, 127.6, 127.5, 125.3, 125.5, 110.0, 87.1, 87.0, 85.5, 77.3, 76.5, 75.1, 73.1, 69.4, 64.9, 40.6, 34.4, 33.7, 31.2, 29.9, 27.8, 27.6, 27.5, 26.3, 24.9, 24.3, 23.3, 23.2, 22.4, 22.0, 18.1, 16.5.



(*R*)-**20**

^{1}H NMR (500 MHz, C_6D_6, δ): 7.43 (d, *J* = 7.6 Hz, 2H); 7.39 (d, *J* = 7.0 Hz, 2H); 7.22 (m, 4H); 7.12 (m, 2H); 5.36 (t, *J* = 6.6 Hz, 1H); 5.25 (t, *J* = 6.4 Hz, 1H); 5.20 (s, 1H); 4.93 (s, 1H); 4.91 (d, *J* = 11.8 Hz, 1H); 4.66 (d, *J* = 11.8 Hz, 1H); 4.51 (q, *J* = 11.9 Hz, 2H); 3.99 (dd, *J* = 5.7, 9.8 Hz, 1H); 3.91 (d, *J* = 10.8 Hz, 1H); 3.43 (dd, *J* = 2.8, 9.5 Hz, 1H); 3.31 (s, 1H); 2.38 (m, 4H); 2.15 (m, 6H); 1.90-1.30 (m, 10H); 1.68 (s, 6H); 1.57 (s, 3H); 1.22 (s, 3H); 1.21 (s, 3H); 1.20 (s, 3H); 1.16 (s, 3H).
^{13}C NMR (125 MHz, C_6D_6, δ): 151.3, 141.3, 140.6, 135.2, 131.5, 128.9, 128.8, 128.1, 127.8, 127.6, 127.5, 126.0, 125.4, 109.7, 87.1, 87.0, 85.8, 77.2, 76.5, 75.3, 72.6, 72.3, 64.9, 41.7, 40.6, 33.6, 31.4, 31.3, 30.5, 29.3, 27.8, 27.6, 26.3, 24.9, 23.2, 22.2, 22.0, 18.1, 16.5, 15.5.

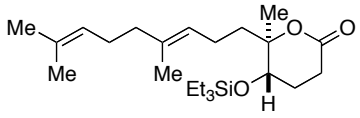
1D nOe experiment suggested there was nOe interaction between the methyl group on the pyran and the allylic proton on the pyran (*R*)-**20**.



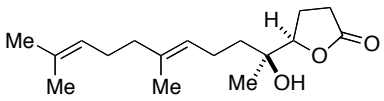
22

Aldehyde **8** (600 mg, 2.269 mmol, 100 mol%) was dissolved in 2-methyl-2-butene (60 mL, ~25 mL/mmol of aldehyde) at room temperature in a 250 mL Erlenmeyer flask. *tert*-butyl alcohol (60 mL) and water (30 mL) were added. $NaH_2PO_4 \bullet H_2O$ (1.252 g, 9.076 mmol, 400 mol%) was added and the mixture was stirred vigorously at rt for 5 min until the mixture became homogeneous. Sodium chlorite (1.231g, 13.616 mmol, 600 mol%) was added in one portion. The mixture was stirred vigorously at rt for 1 h. The mixture was poured into 5% aqueous NaH_2PO_4 solution (200 mL) and extracted twice with diethylether (100 mL then 150 mL). The organic fraction was dried with $MgSO_4$. NMR of the crude reaction mixture showed the desired acid **22** and no cyclization product. The crude mixture was used directly in the next step.

^{1}H NMR (400 MHz, C_6D_6, δ): 5.23 (t, *J* = 6.7 Hz, 1H); 5.16 (t, *J* = 7.1 Hz, 1H); 2.59 (t, *J* = 6.7 Hz, 1H); 2.4-2.0 (m, 9H); 1.69 (s, 3H); 1.60 (m, 1H); 1.58 (s, 3H); 1.56 (s, 3H); 1.40 (m, 1H); 1.08 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 179.0, 135.8, 131.6, 125.2, 124.6, 62.2, 61.0, 40.5, 39.3, 31.5, 27.5, 26.2, 24.7, 24.5, 18.1, 17.0, 16.4.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{28}O_3Na$, 303.1931; found, 303.1929.
$[\alpha]^{20}_D$ –8.4 (*c* 2.97, CH_2Cl_2)



δ-lactone **39** (TES)

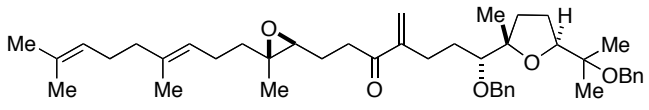


γ-lactone (OH)

Crude Acid **22** (~2.269 mmol, 100 mol%, used directly without purification) was dissolved in dichloromethane (45 mL). The solution was cooled to –78 ˚C. BF_3•OEt_2 was diluted in dichloromethane (5 mL) and added to the reaction mixture over 2 min. Temperature of the cold bath was maintained under –70 ˚C for 8 h. Acetone was added to the cold bath to warm the bath to –50 ˚C over 5 min. The reaction was quenched with saturated $NaHCO_3$ (20 mL). The flask was removed from the cold bath and warmed to room temperature. The mixture was extracted with dichloromethane. The organic layer was dried with $MgSO_4$. ^{1}H NMR of the crude mixture indicated δ-lactone **39** : γ-lactone ratio of 95:5. Column chromatography separated the γ-lactone from δ-lactone **39** (OH). δ-lactone **39** (OH) and imidazole (232 mg, 3.404 mmol, ~150 mol%) were dissolved in *N*,*N*-dimethylformamide (12 mL). Under argon, chlorotriethylsilane (0.460 mL, 2.723 mmol, ~120 mol%) was added in one portion at room temperature. The solution was heated at 50˚C-50˚C for 4h. The reaction was removed from the oil bath and cooled to rt. The reaction was quenched with water (5 mL, exothermic). The mixture was diluted with diethylether (100 mL) and washed twice with saturated NH_4Cl. The organic fraction was dried with $MgSO_4$. Column chromatography isolated 658 mg of δ-lactone **39** (TES) (73% yield over three steps from aldehyde).

δ-lactone **39** (TES):
^{1}H NMR (400 MHz, C_6D_6, δ): 5.23 (t, *J* = 6.8 Hz, 1H); 5.20 (t, *J* = 7.1 Hz, 1H); 3.51 (dd, *J* = 4.6, 7.2 Hz, 1H); 2.42 (dt, *J* = 7.3, 18 Hz, 1H); 2.30-2.00 (m, 7H); 1.68 (s, 3H); 1.60 (s, 3H); 1.57 (s, 3H); 1.60-1.40 (m, 4H); 1.21 (s, 3H); 0.89 (t, *J* = 8.0 Hz, 9H); 0.44 (q, *J* = 7.8 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.8, 136.1, 131.6, 125.2, 124.5, 85.2, 69.6, 40.52, 40.49, 27.5, 27.1, 26.2, 25.7, 22.6, 21.3, 18.1, 16.4, 7.4, 5.6.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{23}H_{42}O_3SiNa$, 417.2795; found, 417.2802.
IR (NaCl, thin film): 2957, 2914, 2877, 1738, 1457, 1378, 1239, 1098, 1006, 745.
$[\alpha]^{20}_D$ +18.0 (*c* 2.83, CH_2Cl_2)

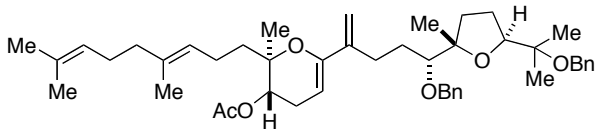
γ-lactone **39b** (OH):
^{1}H NMR (400 MHz, C_6D_6, δ): 5.23 (t, *J* = 6.7 Hz, 1H); 5.17 (t, *J* = 7.0 Hz, 1H); 3.68 (t, *J* = 7.4 Hz, 1H); 2.20-1.70 (m, 8H); 1.68 (s, 3H); 1.58 (s, 3H); 1.57 (s, 3H); 1.45-1.10 (m, 4H); 1.08 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 176.8, 135.8, 131.7, 125.1, 125.0, 85.5, 72.8, 40.5, 37.8, 29.1, 27.5, 26.2, 23.5, 22.5, 22.1, 18.1, 16.4.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{17}H_{28}O_3Na$, 303.1931; found, 303.1939.
IR (NaCl, thin film): 3460, 2967, 2928, 1776, 1452, 1377, 1194, 992.
$[\alpha]^{20}_D$ –2.7 (*c* 3.70, CH_2Cl_2)



23

Epoxy-alcohol **7** (20 mg, 0.02972 mmol, 100 mol%), triethylamine (17 μL, 400 mol%), DMSO (21 μL, 1000 mol%) were dissolved in DCM and cooled in an ice / water bath. SO_3·pyr (9.5 mg, 200 mol%) was added in one portion. The cold bath was allowed to be warmed gradually to rt. The mixture was stirred for 3 d. The mixture was diluted in DCM, washed with water, and dried with $MgSO_4$. Column chromatography isolated 8 mg of **23** (40% yield).

^{1}H NMR (400 MHz, C_6D_6, δ): 7.44 (d, *J* = 7.0 Hz, 2H); 7.40 (d, *J* = 7.0 Hz, 2H); 7.23 (q, *J* = 7.3 Hz, 4H); 7.12 (m, 2H); 5.55 (s, 1H); 5.33 (s, 1H); 5.22 (m, 2H); 4.88 (d, *J* = 11.6 Hz, 1H); 4.63 (d, *J* = 11.7 Hz, 1H); 4.50 (q, *J* = 11.9 Hz, 2H); 3.96 (dd, *J* = 5.8, 9.8 Hz, 1H); 3.37 (dd, *J* = 2.9, 9.1 Hz, 1H); 2.68 (dd, *J* = 4.6, 7.9 Hz, 1H); 2.57 (m, 3H); 2.12 (m, 7H); 1.96 (m, 1H); 1.86-1.52 (m, 7H); 1.67 (s, 3H); 1.57 (s, 6H); 1.45 (m, 2H); 1.21 (s, 3H); 1.19 (s, 3H); 1.17 (s, 3H); 1.14 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 200.2, 149.5, 141.3, 140.5, 135.7, 131.6, 128.9, 127.9, 127.6, 127.5, 125.2, 124.7, 123.9, 86.9, 85.4, 76.5, 74.9, 64.9, 62.7, 61.0, 40.5, 39.5, 35.2, 33.7, 31.6, 29.2, 27.8, 27.5, 26.2, 24.7, 24.5, 24.3, 23.1, 22.1, 18.1, 17.2, 16.4.

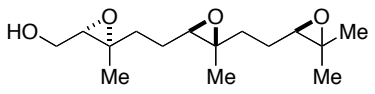


23-DHP

Enone **23** (~5 mg) was dissolved in DCM (1.5 mL). Amberlyst 15 (2 mg) was added at rt. After stirring for 5 h, most enone **23** was consumed. Solid $NaHCO_3$ was added and the mixture was stirred 2h. The mixture was filtered through a cotton plug and concentrated. Column chromatography separated enone **23** from the cyclization product. The cyclization product was dissolved in DCM. Ac_2O, Et_3N and DMAP was added. The mixture was stirred 3 h at rt. After aqueous workup, column chromatography isolated the acetate. Comparison of NMR spectra of the acetate and the alcohol suggested that cyclization of enone **23** in Amberlyst 15 yielded a dihydropyran and not a dihydrofuran.

^{1}H NMR (500 MHz, C_6D_6, δ): 7.43 (d, *J* = 7.4 Hz, 2H); 7.40 (d, *J* = 7.7 Hz, 2H); 7.22 (m, 4H); 7.11 (m, 2H); 5.79 (s, 1H); 5.23 (t, *J* = 6.9 Hz, 2H); 5.12 (t, *J* = 5.9 Hz, 1H); 5.02 (s, 1H); 4.90 (m, 2H); 4.63 (d, *J* = 11.7 Hz, 1H); 4.50 (q, *J* = 11.7 Hz, 2H); 3.98 (dd, *J* = 5.7, 9.8 Hz, 1H); 3.40 (m, 1H); 2.61 (m, 1H); 2.43 (m, 1H); 2.33 (m, 2H); 2.27-1.97 (m, 7H); 1.74 (m, 6H); 1.68 (s, 3H); 1.62 (s, 6H); 1.56 (s, 3H); 1.36 (m, 1H); 1.26 (s, 3H); 1.22 (s, 3H); 1.20 (s, 3H); 1.15 (s, 3H).

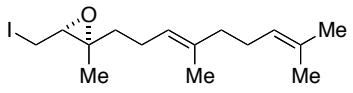
Synthesis of Triepoxide *tert*-Butyl Ester 29 and Epoxide-Opening Cascade



30

Alcohol **15** (1.19 g, 5 mmol, 100 mol%), Bu_4NHSO_4 (0.679 g, 2 mmol, 40 mol%) and (–)-Shi ketone (2.38 g, 10 mmol, 200 mol%) were placed into an 1L Erlenmeyer flask. 1:2 CH_3CN:DMM (200 mL) was added at room temperature. The mixture was cooled in an ice / water bath. Buffer solution (100 mL, 0.05 M $Na_2B_4O_7$•$10H_2O$, in $4x10^{-4}$ M Na_2EDTA solution) was added. K_2CO_3 solution (170 mL, 0.89 M in water) and oxone solution (24.9 g oxone dissolved in $4x10^{-4}$ M Na_2EDTA solution to 170 mL) were added simultaneously over 45 min. After the addition completed the mixture was stirred for 10 min. The mixture was diluted with water to dissolve all solid. The mixture was extracted twice with dichloromethane (500 mL then 300 mL). The dichloromethane extract was dried with $MgSO_4$.
The same procedure was performed three times. The combined crude was purified by column chromatography to yield 3.57 g of **30** (88% yield, average of three runs).

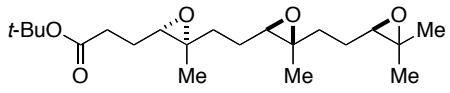
^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.82-3.62 (m, 2H); 2.97 (t, J = 5.8 Hz, 1H); 2.75 (dd, J = 3.7, 7.7 Hz, 1H); 2.69 (t, J = 6.0 Hz, 1H); 2.62 (m, 1H); 1.96-1.48 (m, 8H); 1.30 (s, 3H); 1.291 (s, 3H); 1.289 (s, 3H); 1.25 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 64.0, 63.2, 63.0, 61.0, 60.9, 60.8, 58.7, 36.2, 35.2, 25.0, 24.7, 24.6, 18.8. 16.9, 16.5.
IR (NaCl, thin film): 3442, 2964, 1457, 1386, 1035.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{26}O_4Na$, 293.172; found, 293.173.
$[\alpha]^{20}_D$ +26.2 (*c* 2.10, $CHCl_3$)



30-iodide

Triphenylphosphine (5.83 g, 22.24 mmol, 120 mol%) and imidazole (3.03 g, 44.47 mmol, 240 mol%) were dissolved in 150 mL dichloromethane. The solution was stirred under argon and cooled in an ice/water bath. Iodine (5.64 g, 22.24 mmol, 120 mol%) was added in one portion. Once all iodine was dissolved, alcohol **30** (5.01 g, 18.53 mmol, 100 mol%) in 15 mL dichloromethane was added. The reaction mixture was stirred in the ice/water bath for 30 min. The ice/water bath was removed and the mixture was stirred at rt for 30 min. The mixture was diluted to 200 mL and washed with 2:1 saturated $Na_2S_2O_3$/brine (200 mL). The aqueous layer was extracted again with DCM (100 mL). The organic solution was dried with $MgSO_4$. The solution was concentrated to ~ 20 mL, diluted with 1:1 DCM/hexane, and loaded directly to a silica column that was packed with 1:1 DCM/hexane). Column chromatography isolated 6.1 g of iodide (87% yield).

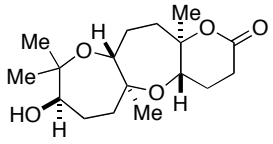
^{1}H NMR (400 MHz, C_6D_6, δ): 2.86 (dd, J = 6.1, 9.7 Hz, 1H); 2.77 (dd, J = 6.2, 7.9 Hz, 1H); 2.61 (dd, J = 7.7, 9.7 Hz, 1H); 2.51 (m, 2H); 1.75-1.33 (m, 8H); 1.13 (s, 3H); 1.08 (s, 3H); 1.06 (s, 3H); 0.93 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 63.7, 63.6, 62.8, 62.5, 60.1, 58.0, 35.9, 35.7, 25.32, 25.30, 25.29, 19.2, 17.2, 16.0, 3.4.
IR (NaCl, thin film): 2963, 2927, 1460, 1385, 1250, 1176, 1121.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{15}H_{25}IO_3Na$, 403.0741; found, 403.0732.
$[\alpha]^{20}_D$ +23.3 (*c* 3.5, CH_2Cl_2)



29

Diisopropylamine (7.53 mL, 53.74 mmol, 335 mmol%) was dissolved in 200 mL THF under argon. The solution was cooled to –78 ˚C and *n*-BuLi (19.9 mL, 49.72 mmol, 2.5M in hexane, 310 mol%) was added in one portion. The mixture was stirred at –78 ˚C for 1.5 h. *tert*-Butylacetate (6.92 mL, 51.33 mmol, 320 mol%) was added. The reaction mixture was stirred for another 1.5 h at –78 ˚C. Iodide from alcohol **30** (6.10 g, 16.04 mmol, 100 mol%) in THF (20 mL) was added to the reaction mixture. After 10 min at –78 ˚C HMPA (8.02 mL, 0.5 mL / mmol iodide) was added. The mixture was stirred for 35 min at –78 ˚C and quenched with saturated NH_4Cl. The reaction was removed from the cold bath and allowed to warm to rt. The mixture was diluted with Et_2O, washed with saturated NH_4Cl, and dried with $MgSO_4$. Column chromatography isolated 5.25 g of triepoxide *tert*-butylacetate **29** (88% yield).

^{1}H NMR (400 MHz, C_6D_6, δ): 2.64 (dd, J = 5.5, 7.1 Hz, 1H); 2.70- 2.45 (m, 2H); 2.35-2.20 (m, 2H); 1.85-1.62 (m, 3H); 1.58-1.42 (m, 7H); 1.37 (s, 9H); 1.14 (s, 3H); 1.09 (s, 3H); 1.08 (s, 3H); 1.06 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 172.3, 80.2, 63.7, 62.7, 62.6, 60.5, 60.0, 57.9, 36.3, 35.9, 32.9, 28.4, 25.4, 25.3, 25.1, 19.1, 17.2, 16.9.
IR (NaCl, thin film): 2965, 1728, 1462, 1367, 1153.
HRMS-ESI (m / z): $[M + Na]^+$ calcd for $C_{21}H_{36}O_5Na$, 391.2455; found, 391.2465.
$[\alpha]^{20}_D$ +4.3 (*c* 5.6, CH_2Cl_2)

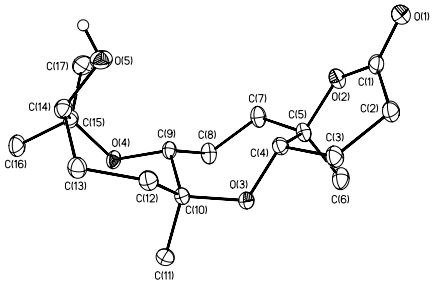


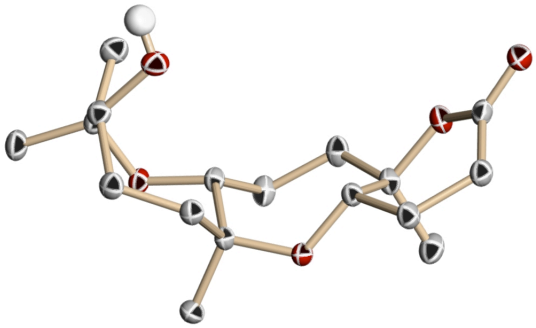
31

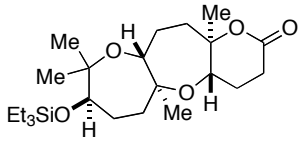
Ester **29** (5.15 g, 13.98 mmol, 100 mol%) and 1,2,3-trimethoxybenzene (4.7 mg, 26.95 mmol, 200 mol%) were dissolved in DCM (280 mL). The mixture was cooled under argon to –78 ˚C. BF_3•OEt_2 (1.77 mL, 13.98 mmol, 100 mol%) was added. The mixture was stirred at –78 ˚C for 1 h and quenched with saturated $NaHCO_3$ (50 mL) at –78 ˚C. The cold bath was removed and the mixture was warmed to rt. Layers were separated and the aqueous layer was extracted two times with DCM (2 x 100 mL). The extract was dried with $MgSO_4$. Column chromatography isolated cyclization product **31** in a concentrated DCM solution (~ 3-5 mL) and carried on directly to the next step.

^{1}H NMR (400 MHz, C_6D_6, δ): 4.14 (d, *J* = 8.9 Hz, 1H); 3.64 (dd, *J* = 5.1, 11.7 Hz, 1H); 3.40 (t, *J* = 5.1 Hz, 1H); 2.27 (dt, *J* = 3.5, 12.8 Hz, 1H); 2.16-2.00 (m, 2H); 1.90-1.45 (m, 10H); 1.26 (s, 3H); 1.20 (s, 3H); 1.13 (s, 3H); 0.97 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 169.3, 84.8, 80.5, 78.4, 76.7, 76.5, 68.7, 42.1, 31.9, 29.2, 29.1, 28.8, 26.1, 25.4, 22.9, 20.9, 20.7.
IR (NaCl, thin film): 3470, 2976, 2941, 1722, 1381, 1273, 1206, 1083.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{17}H_{28}O_5Na$, 335.1829; found, 335.1833.
$[\alpha]^{20}_D$ –3.1 (*c* 1.3, CH_2Cl_2)

ORTEP diagrams of **31**:





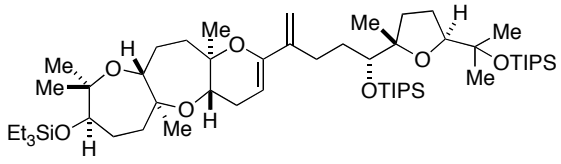


32

Alcohol **31** solution in DCM (~3-5 mL) from the previous step and imidazole (3 g, 44.07 mmol) were dissolved in DMF (20 mL) and fitted with a condenser. The reaction setup was purged with argon. Chlorotriethylsilane (3.0 mL, 17.87 mmol) was added to the reaction mixture at rt. The mixture was heated for 16 h at 45 ˚C and then quenched with MeOH (3 mL). The mixture was stirred for 45 min at 45 ˚C. The mixture was cooled to rt. The mixture was diluted with Et_2O, washed with saturated NH_4Cl and dried with $MgSO_4$. Column chromatography isolated 1.53 g of silyl ether **32** (25% from ester **29**).

^{1}H NMR (400 MHz, C_6D_6, δ): 4.18 (d, *J* = 9.1 Hz, 1H); 3.74 (dd, *J* = 5.0, 11.9 Hz, 1H); 3.55 (d, *J* = 6.7 Hz, 1H); 2.35-2.10 (m, 3H); 2.85-1.25 (m, 9H); 1.26 (s, 3H); 1.18 (s, 3H); 1.16 (s, 3H); 0.96 (s, 3H); 0.93 (t, *J* = 8.0 Hz, 9H); 0.47 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.0, 84.6, 80.3, 78.7, 78.0, 76.3, 69.3, 42.5, 32.0, 29.8, 28.9, 28.7, 26.6, 25.7, 23.6, 20.9, 20.7, 7.6, 5.5.
IR (NaCl, thin film): 2952, 1740, 1380, 1267, 1083, 738.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{42}O_5SiNa$, 449.2694; found, 449.2698.

Foramtion of Cyclic Enol Ether 42

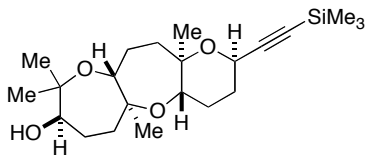


42

Ketone **41** was dissolved in DCM at room temperature. PPTS was added and the mixture was stirred until most of ketone **41** was consumed.

^{1}H NMR (400 MHz, C_6D_6, δ): 5.78 (s, 1H); 5.13 (s, 1H); 5.11 (m, 1H); 4.32 (d, *J* = 9.2 Hz, 1H); 4.01 (dd, *J* = 6.8, 9.6 Hz, 1H); 3.92 (t, *J* = 5.0 Hz, 1H); 3.86 (dd, *J* = 6.3, 8.9 Hz, 1H); 3.61 (d, *J* = 6.7 Hz, 1H); 2.70 (m, 1H); 2.40 (m, 4H); 2.27-1.77 (m, 9H); 1.63 (m, 4H); 1.42 (s, 3H); 1.33 (s, 3H); 1.32 (s, 3H); 1.29 (s, 3H); 1.26 (s, 6H); 1.16 (m, 42 H); 1.02 (s, 3H); 0.98 (t, *J* = 7.9 Hz, 9H); 0.50 (q, *J* = 8.0 Hz, 6H).

Diastereoselective Reactions with Lactone 32

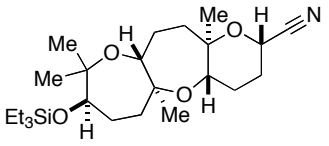


43

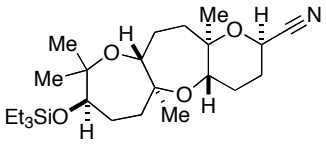
Trimethylsilylacetylene (31 μL, 0.2250 mmol, 400 mol%) was dissolved in THF (1 mL). The solution was cooled at –78 ˚C and *n*-BuLi (90 μL, 0.2250 mmol, 400 mol%) was added. The mixture was stirred at –78 ˚C for 5 min and then warmed in an ice/water bath for 15 min. The mixture was cooled to –78 ˚C again. $BF_3{\cdot}OEt_2$ (29 μL, 0.2250 mmol, 400 mol%) was added. After 30 min at –78 ˚C lactone **32** in THF (1.5 mL) was added to the mixture over 1 min. The mixture was stirred 45 min at –78 ˚C and quenched with saturated $NaHCO_3$. The mixture was removed from the cold bath and quickly melted the solid. The mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ twice, and dried with $MgSO_4$.

The mixture was concentrated and diluted in DCM (1 mL) and CH_3CN (0.2 mL). Triethylsilane (0.1 mL) and $BF_3{\cdot}OEt_2$ (15 μL) were added to the crude at rt. The mixture was stirred 30 min and quenched with saturated $NaHCO_3$. The mixture was diluted with DCM, washed with $NaHCO_3$, and dried with $MgSO_4$. Column chromatography isolated 10 mg of propargyl ether **43** (45% from lactone **32**). The stereochemistry of the propargyl ether was established by a NOSEY experiment.

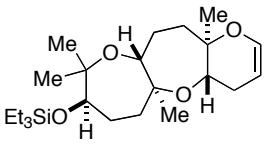
^{1}H NMR (400 MHz, C_6D_6, δ): 4.21-4.15 (m, 2H); 3.56 (dd, J = 5.1, 11.3 Hz, 1H); 3.30 (t, J = 4.5 Hz, 1H); 2.30-1.39 (m, 12H); 1.30 (s, 3H); 1.27 (m, 1H); 1.11 (s, 3H); 0.94 (s, 3H); 0.16 (s, 9H).
^{13}C NMR (100 MHz, C_6D_6, δ): 107.1, 88.0, 80.0, 78.7, 78.0, 77.0, 76.6, 70.8, 61.5, 42.5, 33.4, 29.5, 28.9, 28.6, 26.2, 22.7, 21.0, 16.2, 0.4.



44



45



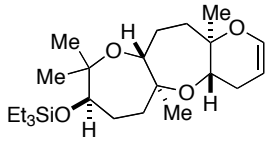
32-cyclic enol ether

Lactone **32** (1.50 g, 3.516 mmol, 100 mol%) was dissolved in toluene (50 mL) and cooled to –78 ˚C under argon. DIBAL (5.27 mL, 5.274 mmol, 1M in toluene) was diluted in toluene (15 mL) and the diluted DIBAL solution was added to the lactone solution over 40 min. After addition completed the reaction was stirred an extra 5 min. The reaction mixture was quenched with methanol (5.3 mL) and the mixture was stirred 10 min. The cold solution was poured into saturated Rochelle's salt solution (200 mL), diluted with Et_2O (100 mL), and stirred vigorously for 1 h. Layers were separated and the aqueous layer was extracted with diethylether. The organic mixture was dried with $MgSO_4$ and concentrated. The crude hemiacetal was used directly.

The crude hemiacetal was dissolved in dichloromethane (35 mL) and cooled to –12 ˚C under argon. Trimethylsilylcyanide (2.2 mL, 17.58 mmol, 500 mol%) was added, followed by $BF_3{\cdot}OEt_2$ (0.67 mL, 5.274 mmol, 150 mol%). The mixture was stirred 45 min and the temperature gradually rose to –5 ˚C. The reaction was quenched with 1:1:1 DCM/MeOH/Et_3N (35 mL) and stirred 15 min at –5 ˚C. The mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, and dried with $MgSO_4$. Column chromatography isolated 600 mg of **44** (39%), 190 mg of **45** (12%), and 420 mg of cyclic enol ether (29%). NOSEY of **44** was consistent with its configuration. Configuration of **45** was confirmed from NOSEY of methyl ketone **53**.

44 (anti H / Me):
^{1}H NMR (400 MHz, C_6D_6, δ): 4.18 (d, *J* = 10.2 Hz, 1H); 4.00 (d, *J* = 4.5 Hz, 1H); 3.56 (d, *J* = 6.8 Hz, 1H); 3.40 (dd, *J* = 4.5, 11.6 Hz, 1H); 2.16 (dt, *J* = 2.8, 13.2 Hz, 1H); 2.00-1.70 (m, 3H); 1.61 (s, 3H); 1.70-1.31 (m, 8H); 1.30 (s, 3H); 1.18 (s, 3H); 0.97 (s, 3H); 0.96 (t, *J* = 7.9 Hz, 9H); 0.50 (q, *J* = 7.8 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 120.7, 80.8, 80.2, 78.5, 78.1, 76.4, 71.2, 59.6, 42.8, 32.3, 29.8, 29.1, 28.8, 26.6, 25.1, 23.6, 21.0, 18.3, 7.6, 5.4.
IR (NaCl, thin film): 2950, 1458, 1379, 1233, 1100, 729.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{24}H_{43}NO_4SiNa$, 460.2854; found, 460.2860.
$[\alpha]^{20}_D$ +12.9 (*c* 3.1, CH_2Cl_2)

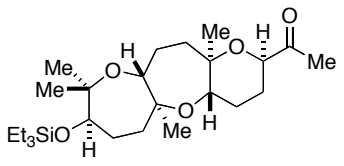
45 (syn H / Me):
^{1}H NMR (400 MHz, C_6D_6, δ): 4.21 (d, *J* = 10.0 Hz, 1H); 3.59 (dd, *J* = 2.4, 12.1 Hz, 1H); 3.56 (d, *J* = 6.8 Hz, 1H); 2.18 (dt, *J* = 2.7, 12.8 Hz, 1H); 1.84 (m, 1H); 1.72-1.38 (m, 8H); 1.32 (m, 1H); 1.30 (s, 3H); 1.21 (s, 3H); 1.17 (m, 1H); 0.98 (s, 3H); 0.96 (t, *J* = 7.9 Hz, 1H); 0.90 (s, 3H); 0.49 (q, *J* = 8.0 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 119.2, 80.1, 79.7, 78.6, 78.0, 76.3, 70.2, 59.6, 42.1, 32.2, 31.1, 29.2, 28.8, 27.6, 26.6, 23.6, 21.0, 15.7, 7.6, 5.5.
IR (NaCl, thin film): 2951, 2877, 1458, 1380, 1244, 1094, 738.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{24}H_{43}NO_4SiNa$, 460.2854; found, 460.2867.
$[\alpha]^{20}_D$ –7.0 (*c* 3.3, CH_2Cl_2)



32-cyclic enol

^{1}H NMR (400 MHz, C_6D_6, δ): 6.23 (d, *J* = 6.1 Hz, 1H); 4.46 (dt, *J* = 2.4, 5.4 Hz, 1H); 4.30 (d, *J* = 9.9 Hz, 1H); 3.95 (dd, *J* = 6.7, 9.4 Hz, 1H); 3.60 (d, *J* = 6.9 Hz, 1H); 2.36 (dt, *J* = 3.0, 13.1 Hz, 1H); 2.30-1.80 (m, 5H); 1.68 (dt, *J* = 2.7, 14.4 Hz, 1H); 1.60 (m, 2H); 1.41 (m, 1H); 1.40 (s, 3H); 1.30 (s, 3H); 1.24 (s, 3H); 1.01 (s, 3H); 0.97 (t, *J* = 7.9 Hz, 9H); 0.50 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 141.7, 97.5, 79.8, 78.7, 78.6, 78.2, 77.2, 68.6, 42.5, 31.9, 29.2, 28.8, 27.8, 26.7, 23.8, 21.2, 17.8, 7.6, 5.5.
IR (NaCl, thin film): 2952, 1656, 1445, 1380, 1248, 1081, 1045, 737.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{42}O_4SiNa$, 433.3745; found, 433.2755.
$[\alpha]^{20}_D$ +9.35 (*c* 3.1, CH_2Cl_2)

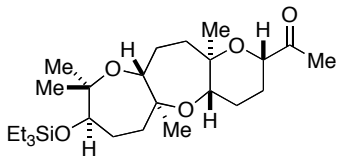
Synthesis of Methyl ketones 50 and 53



53

$Ni(acac)_2$ (4 mg, 0.01578 mmol, 30 mol%) was dissolved in toluene (0.5 mL, saturated with N_2) and cooled in an ice/water bath. Dimethylzinc (80 μL, 0.16 mmol, 300 mol%, 2M in toluene) was added and stirred 15 min. The mixture turned from green to black. Nitrile **45** (23 mg, 0.0526 mmol, 100 mol%) was dissolved in toluene (0.5 mL) and added to the catalyst mixture. The mixture was stirred 18 h at rt. The mixture was cooled in an ice/ water bath, poured into ice-cold HCl solution (2 mL, 0.5M), and rinsed with Et_2O. The mixture was stirred vigorously for 15 min. The mixture was diluted with Et_2O, washed with saturated NH_4Cl, and dried with $MgSO_4$. The crude was >90% pure by NMR (20 mg, 83% yield). NOSEY of **53** was consistent with the assigned configuration.

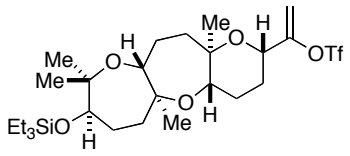
^{1}H NMR (400 MHz, C_6D_6, δ): 4.30 (d, *J* = 10.3 Hz, 1H); 3.68 (dd, *J* = 2.7, 11.8 Hz, 1H); 3.59 (d, *J* = 6.8 Hz, 1H); 3.51 (dd, *J* = 5.0, 11.3 Hz, 1H); 2.25 (dt, *J* = 2.9, 13.0 Hz, 1H); 1.35 (s, 3H); 2.00-1.42 (m, 10 H); 1.39 (m, 1H); 1.36 (s, 3H); 1.24 (s, 3H); 1.09 (s, 3H); 1.00 (s, 3H); 0.97 (t, *J* = 7.9 Hz, 9H); 0.50 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 208.3, 79.9, 78.6, 78.2, 78.1, 76.6, 75.8, 71.2, 43.0, 32.2, 29.4, 28.8, 28.3, 26.7, 25.6, 23.6, 21.1, 16.2, 7.7, 5.5.



50

$Ni(acac)_2$ (9 mg, 0.03384 mmol, 37 mol%) was dissolved in toluene (0.9 mL, saturated with N_2) and cooled to –15 ˚C. Methylmagnesium bromide (200 μL, 0.2744 mmol, 300 mol%, 1.4M in 3:1 THF/toluene) was added and stirred 5 min. The mixture turned from green to black. Nitrile **44** (40 mg, 0.09147 mmol, 100 mol%, dr >95:5) was dissolved in toluene (1.3 mL) and added to the catalyst mixture. The mixture was stirred 30 min and temperature slowly warmed to –8 ˚C. The mixture was cooled in an ice/water bath, poured into ice-cold HCl solution (4 mL, 0.5M), and rinsed with Et_2O. The mixture was stirred vigorously for 15 min. The mixture was diluted with Et_2O, washed with saturated NH_4Cl, and dried with $MgSO_4$. Column chromatography isolated 21 mg of **50** (50% yield, dr 93:7)

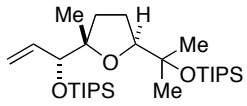
^{1}H NMR (400 MHz, C_6D_6, δ): 4.36 (d, J = 9.9 Hz, 1H); 3.71 (dd, J = 2.4, 6.3 Hz, 1H); 3.68 (m, 1H); 3.65 (d, J = 6.6 Hz, 1H); 2.45-2.25 (m, 2H); 2.06 (s, 3H); 2.12-1.82 (m, 4H); 1.75-1.55 (m, 5H); 1.45 (m, 1H); 1.41 (s, 3H); 1.29 (s, 3H); 1.20 (s, 3H); 1.06 (t, J = 8.1 Hz, 12H); 0.59 (q, J = 7.9 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 209.6, 79.9, 79.6, 78.5, 78.2, 76.7, 76.1, 71.8, 43.1, 32.2, 29.6, 28.8, 26.7, 26.4, 25.3, 24.5, 23.7, 21.1, 18.7, 7.7, 5.5.
IR (NaCl, thin film): 2952, 1719, 1457, 1379, 1243, 1101, 729.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{46}O_5SiNa$, 477.3007; found, 477.3004.
$[\alpha]^{20}_D$ –9.18 (*c* 4.7, CH_2Cl_2)



57

Comin's reagent (40 mg, 0.1016 mmol, 115 mol%) was dissolved in THF (0.5 mL) and cooled to –78 ˚C. LHMDS (0.9 mL, 0.18 mmol, 200 mol%, 0.2M in THF, freshly prepared) was added to the Comin's reagent solution. After stirring for 2 min at –78 ˚C, ketone **50** (40 mg, 0.8835 mmol, 100 mol%) in THF (1 mL) was added. More THF (0.5 mL) was used to rinse the wall of the flask. The mixture was stirred 2.5 h at –78 ˚C and then at 0˚C for 30 min. The crude was diluted with Et_2O and washed with saturated $NaHCO_3$ and then twice with 1M NaOH. The crude was dried with $MgSO_4$ and concentrated. NMR of the crude indicated the presence of the alkenyl triflate **57** and HMDS. The crude was used directly in the next step. (SN081845)

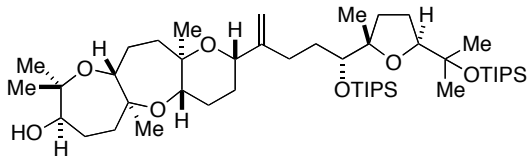
^{1}H NMR (400 MHz, C_6D_6, δ): 4.77 (dd, *J* = 1.1, 4.0 Hz, 1H); 4.54 (dd, *J* = 1.5, 3.9 Hz, 1H); 4.34 (m, 1H); 4.24 (d, *J* = 10.2 Hz, 1H); 3.66 (dd, *J* = 5.0, 11.2 Hz, 1H); 3.57 (m, 1H); 2.25 (t, *J* = 13.1 Hz, 1H); 1.99-1.15 (m, 11H); 1.41 (s, 3H); 1.33 (s, 3H); 1.30 (s, 3H); 1.20 (s, 3H); 1.00 (t, *J* = 8.0 Hz, 9H); 0.53 (q, *J* = 7.8 Hz, 6H).
^{13}C NMR (100 MHz, C_6D_6, δ): 157.7, 104.9, 80.2, 79.6, 78.6, 78.1, 76.5, 71.2, 68.2, 67.8, 42.0, 32.5, 29.4, 28.8, 26.7, 26.1, 24.4, 23.6, 21.1, 19.3, 7.7, 5.5.
^{19}F NMR (376 MHz, C_6D_6, δ): –76.32 (s, 3F). (Referenced with CF_3CH_2OH at –77.8 ppm)
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{26}H_{45}F_3O_7SSiNa$, 609.2500; found, 609.2491.



59

Trimethylsulfonium iodide (102 mg, 0.5 mmol, 500 mol%) was mixed with THF (1 mL) and cooled in an ice / salt bath (–15 °C). *n*-Butyllithium (0.2 mL, 0.5 mmol, 500 mol%, 2.5M in hexane) was added. The reaction mixture was stirred 40 min and the temperature rose to –10 °C. Epoxide **11** (19 mg, 0.1 mmol, 100 mol%) in THF (1 mL) was added to the mixture. The mixture was stirred 3h and gradually warmed to rt. Triisopropylsilane (128 μL, 0.65 mmol, 650 mol%) was added and the mixture was stirred 4h at rt. The reaction was quenched with MeOH (0.2 mL) and stirred 5 min. The mixture was diluted with Et_2O, washed with saturated NH_4Cl, saturated $NaHCO_3$, and dried with $MgSO_4$. Column chromatography isolated mono-TIPS-ether. This intermediate was dissolved in DCM (2 mL). Triethylamine (100 μL) and TIPSOTf (100 μL) were added. The mixture was heated at 45 °C for 24 h. The mixture was quenched with MeOH (0.2 mL) and refluxed for 1h. The mixture was cooled to rt and diluted with Et_2O. The mixture was washed with water, saturated $NaHCO_3$, and dried with $MgSO_4$. Column chromatography isolated 33 mg of **59** (64% yield).

^{1}H NMR (400 MHz, C_6D_6, δ): 5.82 (ddd, *J* = 7.5, 10.4, 17.6 Hz, 1H); 5.16 (d, *J* = 9.7 Hz, 1H); 5.02 (d, *J* = 10.4 Hz, 1H); 4.24 (d, *J* = 7.4 Hz, 1H); 3.98 (dd, *J* = 6.6, 8.8 Hz, 1H); 2.28 (m, 1H); 1.93 (m, 2H); 1.45 (m, 1H); 1.35 (s, 3H); 1.29 (s, 3H); 1.19 (s, 3H); 1.18-1.12 (m, 42H).
^{13}C NMR (100 MHz, C_6D_6, δ): 140.0, 116.8, 88.5, 86.2, 81.1, 75.0, 33.2, 29.3, 27.6, 25.2, 24.8, 19.0, 18.9, 14.1, 13.6.
IR (NaCl, thin film): 2944, 2867, 1464, 1382, 1172, 1097, 1067, 882, 679.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{29}H_{60}O_3Si_2Na$, 535.3973; found, 535.3983.
$[\alpha]^{20}_D$ –2.7 (*c* = 4.5, CH_2Cl_2)

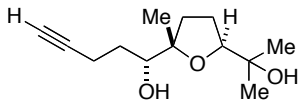


4

9-BBN dimer (24.4 mg, 0.1 mmol, 110 mol%) was placed in a Schlenk tube. Alkene **59** (51.3 mg, 0.1 mmol, 110 mol%) in THF (1 mL) was added under argon at rt. More THF (0.2 mL) was used for rinsing. The Schlenk tube was closed and the mixture was heated at 55 ºC for 20 h. After the mixture was cooled to rt, Cesium carbonate solution (0.2 mL, 0.2 mmol, 220 mol%, 1M in H_2O, saturated with nitrogen) was added under argon. Bubbling occurred immediately. The mixture was stirred at rt for 15 min. Crude alkenyl triflate **57** (~0.08835 mmol, 100 mol%) in THF (1 mL) was added. Pd(dppf)Cl_2 (8 mg, 0.01 mmol, 11 mol%) in DMF (1 mL) was added. The Schlenk tube was closed and the mixture was heated at 55 ºC for 18 h. The reaction was cooled to room temperature. The crude was diluted with Et_2O, washed with 0.5M HCl and brine, and dried with $MgSO_4$. Column chromatography isolated cross coupling products. The mixture of products was dissolved in THF (5 mL) and TBAF (80 μL, 0.08 mmol, 1M THF) was added at rt. The reaction was stirred 1.25 h. The mixture was diluted with Et_2O and washed with H_2O. Column chromatography isolated TES deprotected cross coupling product **4** (19 mg, 26%) and also cross coupling product that has both TES and 2º TIPS group deprotected (**60**) (12 mg, 20%).

^{1}H NMR (600 MHz, C_6D_6, δ): 4.96 (s, 1H); 4.93 (s, 1H); 4.24 (m, 2H); 3.93 (t, *J* = 5.2 Hz, 1H); 3.89 (dd, *J* = 6.4, 9.0 Hz, 1H); 3.81 (dd, *J* = 4.3, 11.5 Hz, 1H); 3.20 (d, *J* = 6.3 Hz, 1H); 2.54 (m, 2H); 2.34 (t, *J* = 12.8 Hz, 1H); 2.24 (q, *J* = 10.4 Hz, 1H); 2.15-1.50 (m, 16H); 1.45 (s, 3H); 1.37 (s, 3H); 1.35 (s, 3H); 1.30 (s, 3H); 1.27 (s, 3H); 1.21 (m, 21H); 1.16 (m, 21H); 1.09 (s, 3H); 0.93 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ):152.9, 109.2, 87.8, 87.1, 80.1, 78.9, 78.7, 78.0, 77.2, 76.8, 74.9, 71.7, 70.8, 42.4, 36.0, 34.3, 32.4, 30.6, 29.9, 29.3, 29.0, 27.6, 27.5, 26.2, 25.42, 25.35, 23.1, 22.6, 21.1, 20.1, 19.11, 19.05, 14.12, 14.08.
IR (NaCl, thin film): 3451, 2943, 2866, 1463, 1380, 1082, 883.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{48}H_{92}O_7Si_2Na$, 859.6274; found, 859.6277.

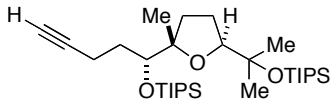
Synthesis of Alkenyl Iodide 35



36

Magnesium turnings (245 mg, 10.07 mmol, 375 mol%), $HgCl_2$ (11 mg, 0.04028 mmol, 1.5 mol%) and I_2 (25 mg, 0.09850 mmol, 3.7 mol%) were purged under argon. Et_2O (8 mL) was added and the mixture was cooled in an ice / water bath. Propargyl bromide (1.2 g, 80% wt solution in toluene, 8.055 mmol, 300 mol%) was added slowly. The brown color disappeared and the addition continued with gentle bubbling. The mixture was stirred in the ice / water bath for 1 h.
In another flask epoxide **11** (500 mg, 2.685 mmol, 100 mol%) was dissolved in Et_2O (45 mL). This solution was cooled to –78 ˚C. Allenyl magnesium bromide as prepared above was transferred to the epoxide solution over 2 min. White precipitate appeared and stirred became difficult. Temperature was kept below –70 ˚C for 1 h and then allowed to warm to rt overnight. After a total of 18 h, starting material was all consumed as judged by GCMS. Reaction was cooled to –78 ˚C and quenched with saturated NH_4Cl. Once the solution was warmed to rt and all solid melted, the solution was diluted with Et_2O and layers were separated. The aqueous layer was extracted again with Et_2O. The organic solution was dried with $MgSO_4$. Column chromatography isolated 200 mg of alkyne **36**, which was mixed with 10% allenyl product (~33% yield).

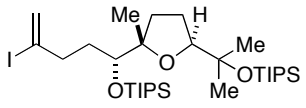
^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.75 (t, J = 8.2 Hz, 1H); 3.62 (d, J = 10.7 Hz, 1H); 2.84 (s, 1H); 2.46-2.25 (m, 3H); 2.06 (m, 1H); 1.93 (t, J = 2.6 Hz, 1H); 1.80 (m, 2H); 1.60 (m, 1H); 1.50 (m, 2H); 1.16 (s, 3H); 1.11 (s, 3H); 1.09 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 87.7, 85.9, 84.4, 75.2, 70.8, 68.6, 31.4, 30.7, 27.6, 26.8, 24.0, 23.8, 15.8.



37

Diol **36** (100 mg, 0.4419 mmol, 100 mol%) was dissolved in CH_2Cl_2 (5 mL) under argon, connected to a condenser. Triethylamine (0.3 mL, 2 mmol, 450 mol%) was added at rt, followed by TIPSOTf (0.29 mL, 1 mmol, 226 mol%). Rinsed the wall of condenser with CH_2Cl_2 (1 mL). The mixture was heated at 45 ˚C for 15 h. Once cooled to rt, the reaction was quenched with water. The mixture was diluted with Et_2O and the layers were separated. The ether layer was washed with saturated $NaHCO_3$ and dried with $MgSO_4$. Column chromatography separated the alkyne **37** (150 mg, 64%) from the allene isomer (84 mg, 36%) from the previous step.

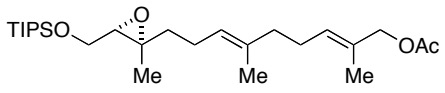
^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.81 (dd, *J* = 5.12, 6.5 Hz, 1H); 3.72 (dd, *J* = 6.5, 8.6 Hz, 1H); 2.37 (dt, *J* = 2.5, 8.3 Hz, 2H); 2.10-1.80 (m, 4H); 1.92 (t, *J* = 2.6 Hz, 1H); 1.76-1.59 (m, 2H); 1.24 (s, 3H); 1.19 (s, 3H); 1.12 (s, 3H); 1.09 (s, 3H); 1.06 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, δ): 87.3, 86.2, 85.3, 76.3, 74.3, 68.2, 36.4, 33.5, 28.7, 26.6, 24.9, 21.7, 18.60, 18.58, 18.56, 15.8, 13.6, 13.4.
IR (NaCl, thin film): 3315, 2945, 2867, 2121, 1464, 1174, 883.
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{31}H_{62}O_3Si_2Na$, 561.4130; found, 561.4125.



35

Alkyne **37** (340 mg, 0.6308 mmol, 100 mol%) was dissolved in anhydrous pentane (6.3 mL) under argon. The solution was cooled in an ice / salt slush bath (–15 °C). *B*-I-9-BBN (660 µL, 0.6623 mmol, 1M in hexane, 105%) was added. The mixture was stirred in the cold bath for 2.5 h. Temperature slowly rose to 10 °C. AcOH (0.3 mL, ~ 0.5 mL / mmol alkyne) added and the mixture was stirred at ~5 °C for 2 h. The mixture was diluted with hexane (200 mL) and washed twice with a 1:1 mixture of sat. $NaHCO_3$ / sat. $Na_2S_2O_3$ solution. The organic fraction was dried with $MgSO_4$. Column chromatography isolated 362 mg of alkenyl iodide **35** and recovered 33 mg of alkyne **37** (86%, 95% yield BRSM).

^{1}H NMR (400 MHz, C_6D_6, δ): 5.87 (s, 1H); 5.60 (s, 1H); 3.81 (t, *J* = 5.7 Hz, 1H); 3.78 (dd, *J* = 6.2, 9.2
Hz, 1H); 2.73 (m, 1H); 2.58 (m, 1H); 2.04 (m, 2H); 1.84 (m, 3H); 1.58 (m, 1H); 1.28 (s, 3H); 1.25 (s,
3H); 1.20-1.12 (m, 45H).
^{13}C NMR (100 MHz, C_6D_6, δ): 125.5, 113.5, 88.0, 86.8, 77.7, 74.7, 43.3, 36.6, 35.5, 29.1, 27.3, 25.5,
22.6, 19.1, 19.03, 19.01, 14.1, 14.0.
IR (NaCl, thin film): 2944, 1617, 1464, 1382, 1172, 1098, 883.
$[\alpha]^{20}_D$ –10.0 (*c* = 3.0, CH_2Cl_2)
HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{31}H_{63}O_3Si_2Na$, 689.3252; found, 689.3274.



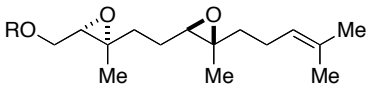
67

Alcohol **15** (11.95 g, 50.13 mmol, 100 mol%) and imidazole (7.5 g, 110 mmol, 220 mol%) were dissolved in DCM (150 mL). TIPSCl (11.8 mL, 55.15 mmol, 110 mol%) was added. The mixture was stirred at rt for 24 h. MeOH (7 mL) was added and the mixture was stirred 2 h at rt. The mixture was diluted with Et_2O, washed with water, and dried with $MgSO_4$. The crude TIPS ether was used directly.

The crude TIPS and salicylic acid (690 mg, 5 mmol, 10 mol%) were dissolved in DCM. *t*-BuOOH (13.6 mL, 75 mmol, ~5.5 M in decane) was added at rt, followed by SeO_2 (277 mg, 2.5 mmol, 5 mol%). The mixture was stirred at rt for 7.5 h. Crude was washed with 1:1 $NaHCO_3/Na_2S_2O_3$. The aqueous layer was extracted with DCM. The organic fraction was dried with $MgSO_4$. Column chromatography separated products from starting material. The recovered starting material (~10 g) was resubjected to the same reaction condition (350 mg salicylic acid, 6 mL *t*-BuOOH, 141 mg SeO_2). A total of ~9.3 g alcohols (a mixture regioisomers of allylic oxidation) were obtained.

The allylic alcohols were dissolved in DCM (120 mL). Triethylamine (7.58 mL) added, followed by Ac_2O (2.57 mL). The mixture was stirred 10 h at rt. More triethylamine (1 mL) and Ac_2O (1 mL) were added and the mixture was stirred for another 12 h. MeOH (5 mL) was added and the mixture was stirred 0.5 h. Volatiles were removed. Column chromatography isolated 7.265 g acetate **67** (32% yield from **15**).

^{1}H NMR (500 MHz, C_6D_6, δ): 5.41 (t, *J* = 6.9 Hz, 1H); 5.14 (t, *J* = 7.1 Hz, 1H); 4.48 (s, 2H); 3.81 (ddd, *J* = 5.4, 11.2, 29.3 Hz, 2H); 3.01 (t, *J* = 5.3 Hz, 1H); 2.11 (m, 4H); 1.96 (m, 2H); 1.71 (s, 3H); 1.60 (m, 1H); 1.55 (s, 3H); 1.50 (s, 3H); 1.45 (m, 1H); 1.16 (s, 3H); 1.10 (m, 21H).
^{13}C NMR (125 MHz, C_6D_6, δ): 170.3, 135.2, 131.0, 129.6, 124.8, 70.4, 63.5, 63.4, 60.1, 39.7, 39.2, 27.0, 24.4, 20.9, 18.7, 17.3, 16.3, 14.3, 12.6.



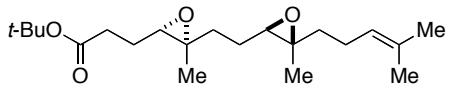
69 (R = TIPS)

Acetate **67** (6.909 g, 14.74 mmol, 100 mol%) was dissolved in THF (150 mL) and MeOH (66 mL). Aqueous LiOH (44 mL, 22 mmol, 150 mol%, 0.5 M) was added at rt. Stirred 45 min at rt. Dilute with 100 mL 0.25M LiOH and brine. The mixture was extracted with DCM and dried with $MgSO_4$. Column chromatography isolated 4.9 g allylic alcohol.

Allylic alcohol (4.8 g, 11.249 mmol, 100 mol%) was dissolved in DCM (100 mL). Triethylamine (3.1 mL, 22.50 mmol, 200 mol%) was added. The mixture was cooled to –78 ºC. MsCl (1 mL, 12.94 mmol, 115 mol%) was added. The mixture was stirred 45 min at –78 ºC and –15 ºC to 0 ºC for another 45 min. LiBr (2.44 g, 28.13 mmol, 250 mol%) in THF (11 mL) was added. The mixture was stirred 45 min from 0 ºC to rt. The mixture was diluted with Et_2O and washed with brine. The aqueous layer was extracted with Et_2O. The ether solution was dried with $MgSO_4$. The crude mesylate was concentrated and used directly.

The crude mesylate was dissolved in THF (150 mL) and cooled to –78 ºC. $LiBEt_3H$ (22.5 mL, 22.5 mmol, 200 mol%, 1M THF) was added. The mixture was stirred at –78 ºC for 1h. The reaction was vented with a needle. Water was added dropwise with mild bubbling observed. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et_2O, washed with brine and dried with $MgSO_4$. Column chromatography isolated 2.9 g alkene **69** (49% yield from acetate **67**).

^{1}H NMR (400 MHz, C_6D_6, δ): 5.12 (t, *J* = 7.2 Hz, 1H); 3.81 (d, *J* = 5.1 Hz, 2H); 2.97 (t, *J* = 5.2 Hz, 1H); 2.53 (m, 1H); 2.07 (m, 2H); 1.65 (s, 3H); 1.63-1.20 (m, 6H); 1.53 (s, 3H); 1.10 (m, 27H).
^{13}C NMR (100 MHz, C_6D_6, δ): 131.8, 124.9, 63.7, 63.5, 63.0, 60.3, 59.8, 39.5, 36.2, 26.2, 25.4, 24.6, 18.6, 18.0, 17.2, 17.0, 12.6.



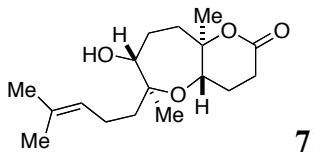
65

Alkene **69** (400 mg, 0.9739 mmol, 100 mol%) was dissolved in THF (3 mL). TBAF (2 mL, 2 mmol, 200 mol%) was added at rt. After 6h at rt, the reaction was quenched with water. The mixture was diluted with Et_2O, washed with H_2O and dried with $MgSO_4$. After removal of solvents, the crude **70** was used directly.

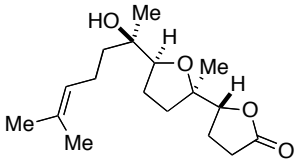
Triphenylphosphine (307 mg, 1.169 mmol, 120 mol%) and imidazole (159 mg, 2.337 mmol, 240 mol%) were dissolved in DCM (5 mL) under argon. The mixture was cooled in an ice / water bath. Iodine (297 mg, 1.169 mmol, 120 mol%) was added in one portion. After most iodide dissolved, alcohol **70** (~0.9739 mmol, crude) in DCM (6 mL) was added. The mixture was stirred in an ice / water bath for 0.5 h and then room temperature for 0.5 h. Most DCM was removed by rotavap. The crude was loaded directly to a silica column (packed in 10% DCM / hexane). Column chromatography isolated the iodide in 86% yield from silyl ether **69**.

Diisopropylamine (0.37 mL, 2.621 mmol, 310 mol%) was dissolved in THF (9 mL) and cooled at –78 ºC. *n*-BuLi (1 mL, 2.5 mmol, 300 mol%, 2.5 M in hexane) was added. The mixture was stirred 30 min at –78 ºC. *tert*-Butyl acetate (353 μL, 2.621 mmol, 310 mol%) was added. The mixture was stirred 45 min at –78 ºC. Iodide (308 mg, 0.8455 mmol, 100 mol%) in THF (6 mL) was added. After 5 min HMPA (423 μL, 0.5 mL / mmol iodide) was added. The mixture was stirred 40 min at –78 ºC. The mixture was quenched with sat. NH_4Cl. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et_2O, washed with NH_4Cl, and dried with $MgSO_4$. Column chromatography isolated **65** in 82% yield.

^{1}H NMR (400 MHz, C_6D_6, δ): 5.12 (t, *J* = 7.1 Hz, 1H); 2.63 (t, *J* = 6.6 Hz, 1H); 2.53 (m, 1H); 2.26 (m, 2H); 2.39 (m, 2H); 1.90-1.20 (m, 8H); 1.64 (s, 3H); 1.53 (s, 3H); 1.36 (s, 9H); 1.11 (s, 3H); 1.06 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 172.3, 131.8, 124.9, 80.2, 63.1, 62.6, 60.5, 60.3, 39.5, 36.4, 32.9, 28.4, 26.2, 25.5, 25.1, 24.6, 18.0, 17.0, 16.9.



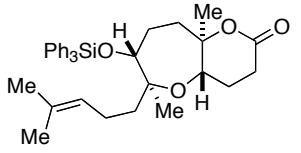
71



72

Diepoxide **65** (40 mg, 0.1135 mmol, 100 mol%) and (1,2,3)-trimethoxybenzene (38 mg, 0.2269, 200 mol%) were dissolved in DCM (3 mL) and cooled to –78 ºC. BF_3•OEt_2 (14 μL, 0.1135 mmol, 100 mol%) was diluted in DCM (0.5 mL) and added to the mixture over 1 min. The mixture was stirred at –78 ºC for 1h. The mixture was quenched with sat. $NaHCO_3$. The mixture was removed from the cold bath. Once solid melted the mixture was diluted with Et_2O, washed with $NaHCO_3$, and dried with $MgSO_4$. Column chromatography isolated **71** and **72** as inseparable mixture in 30% yield. NOSEY of **71** established its configuration as shown.

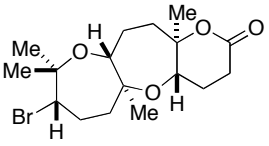
71:
^{1}H NMR (400 MHz, C_6D_6, δ): 5.24 (t, *J* = 5.9 Hz, 1H); 3.26 (d, *J* = 10.2 Hz, 1H); 3.12 (dd, *J* = 5.4, 11.6 Hz, 1H); 2.15 (m, 3H); 1.98 (m, 1H); 1.80-1.00 (m, 8H); 1.72 (s, 3H); 1.58 (s, 3H); 1.12 (s, 3H); 1.09 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.8, 131.5, 125.7, 83.9, 80.3, 79.2, 69.0, 41.6, 37.8, 29.6, 29.0, 26.3, 25.0, 23.2, 20.4, 19.2, 18.1.



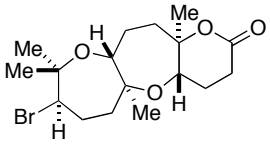
73

The mixture of **71** and **72** (12 mg, 0.04049 mmol, 100 mol%) and imidazole (11 mg, 0.1620 mmol, 400 mol%) were dissolved in DCM (3 mL). Ph_3SiCl (24 mg, 0.08097 mmol, 200 mol%) was added. The mixture was stirred at rt for 14 h. MeOH (0.25 mL) was added and stirred another 1h. The mixture was diluted with Et_2O, washed with water, and dried with $MgSO_4$. Column chromatography (packed with toluene) in 2-5% Et_2O / toluene eluted **73** (16 mg) with a small amount of Ph_3Si protected **72**. Flushing the column with 50% EtOAc / hexane eluted **72** (3 mg). The structure of **73** was confirmed with a NOSEY experiment.

73:
^{1}H NMR (600 MHz, C_6D_6, δ): 7.73 (m, 6H); 7.20 (m, 9H); 5.19 (t, *J* = 7.1 Hz, 1H); 3.75 (d, *J* = 10.3 Hz, 1H); 2.92 (dd, *J* = 5.4, 11.6 Hz, 1H); 2.18 (m, 2H); 2.04 (ddd, *J* = 1.7, 7.7, 18.4 Hz, 1H); 1.90 (m, 1H); 1.81 (m, 1H); 1.71-1.10 (m, 7H); 1.70 (s, 3H); 1.57 (s, 3H); 1.37 (s, 3H); 1.06 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.1, 136.2, 135.2, 130.9, 128.7, 125.5, 83.1, 82.2, 80.7, 69.0, 41.1, 37.4, 29.2, 28.7, 26.2, 24.9, 23.1, 20.4, 20.2, 18.1.



66

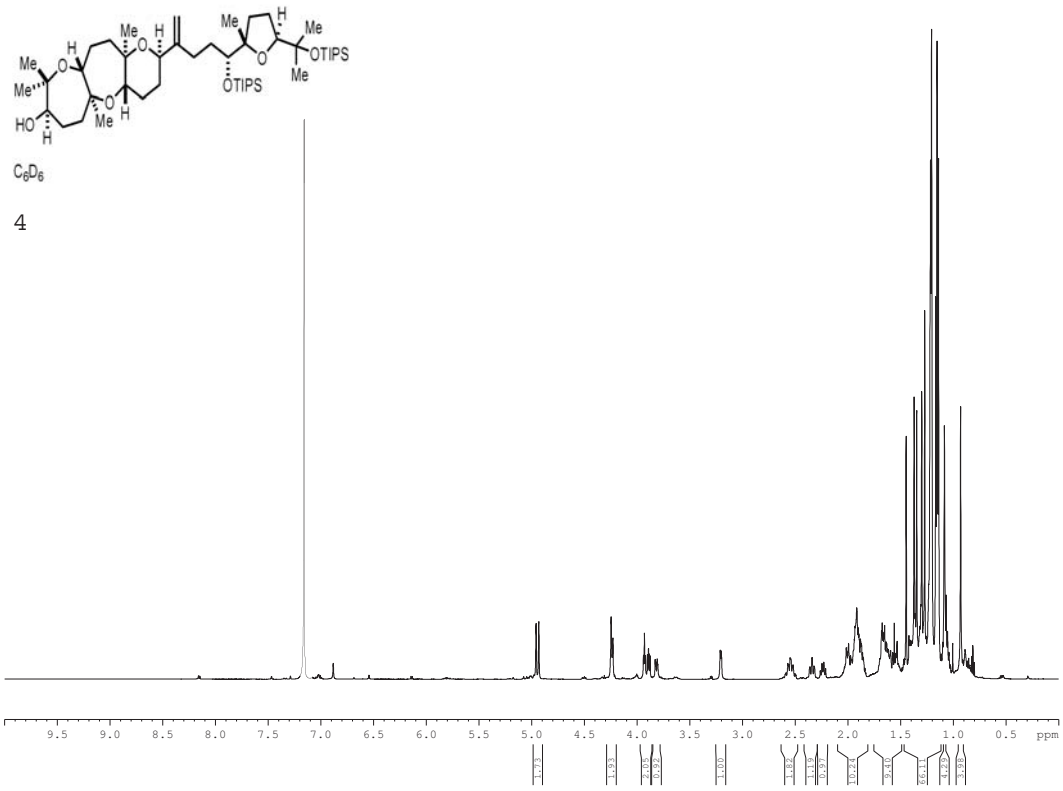


epi-**66**

To alcohol **71** (9 mg, 0.03036 mmol, 100 mol%) and 4Å molecular sieves (50 mg) was added 1,1,1,3,3,3-hexafluoropropan-2-ol (1 mL) under argon. The slurry was cooled in an ice / water bath. NBS (6 mg, 0.03340 mmol, 110 mol%) was added and the mixture was stirred 10 min. More NBS (4 mg) added and stirred another 5 min. Solvent evaporated and the crude was loaded directly to a silica column (packed in 5% ethyl acetate / hexane). Column chromatography isolated ~ 5 mg (43%) bromides as a 63:37 mixture of diastereomers **66** and *epi*-**66**. A NOSEY experiment indicated that the major diastereomer was **66**.

66:
^{1}H NMR (400 MHz, C_6D_6, δ): 3.82 (m, 1H); 3.03 (dd, *J* = 5.4, 11.6 Hz, 1H); 2.96 (d, *J* = 10.2 Hz, 1H); 2.40-0.50 (m, 12H); 1.33 (s, 3H); 1.16 (s, 3H); 1.05 (s, 3H); 1.02 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.1, 84.0, 79.5, 78.2, 76.2, 68.6, 59.7, 41.7, 39.7, 32.0, 29.2, 28.2, 25.8, 25.3, 25.0, 21.0, 20.5.

epi-**66**:
^{1}H NMR (400 MHz, C_6D_6, δ): 4.09 (m, 1H); 4.01 (m, 1H); 3.60 (dd, *J* = 5.1, 11.7 Hz, 1H); 2.40-0.50 (m, 12H); 1.26 (s, 3H); 1.13 (s, 3H); 1.11 (s, 3H); 0.87 (s, 3H).
^{13}C NMR (100 MHz, C_6D_6, δ): 168.1, 84.2, 80.1, 76.9, 76.1, 69.6, 66.6, 42.0, 35.2, 29.7, 29.4, 28.7, 28.6, 28.4, 25.6, 21.5, 20.6.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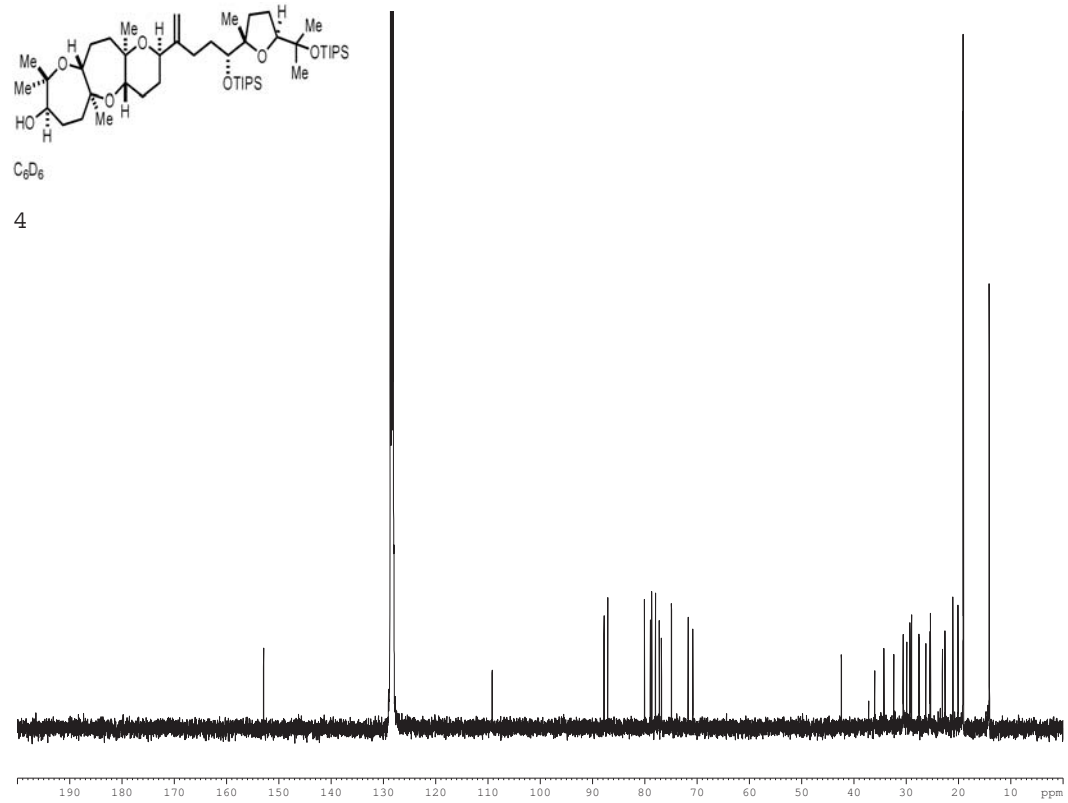
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4
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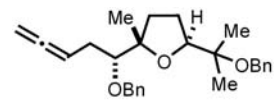

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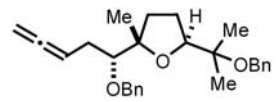

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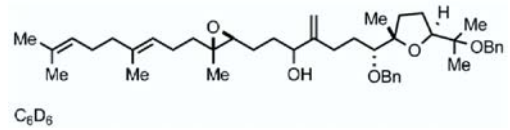
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Me
Me
O
OH
OBn
Me
H
O
Me
OBn
Me
C6D6

7

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8.5
8.0
7.5
7.0
6.5
6.0
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2.0
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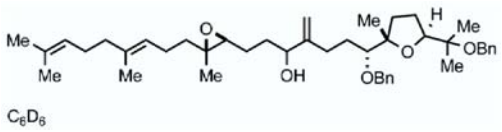
0.5
ppm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OBn
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H
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OBn
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C6D6

7

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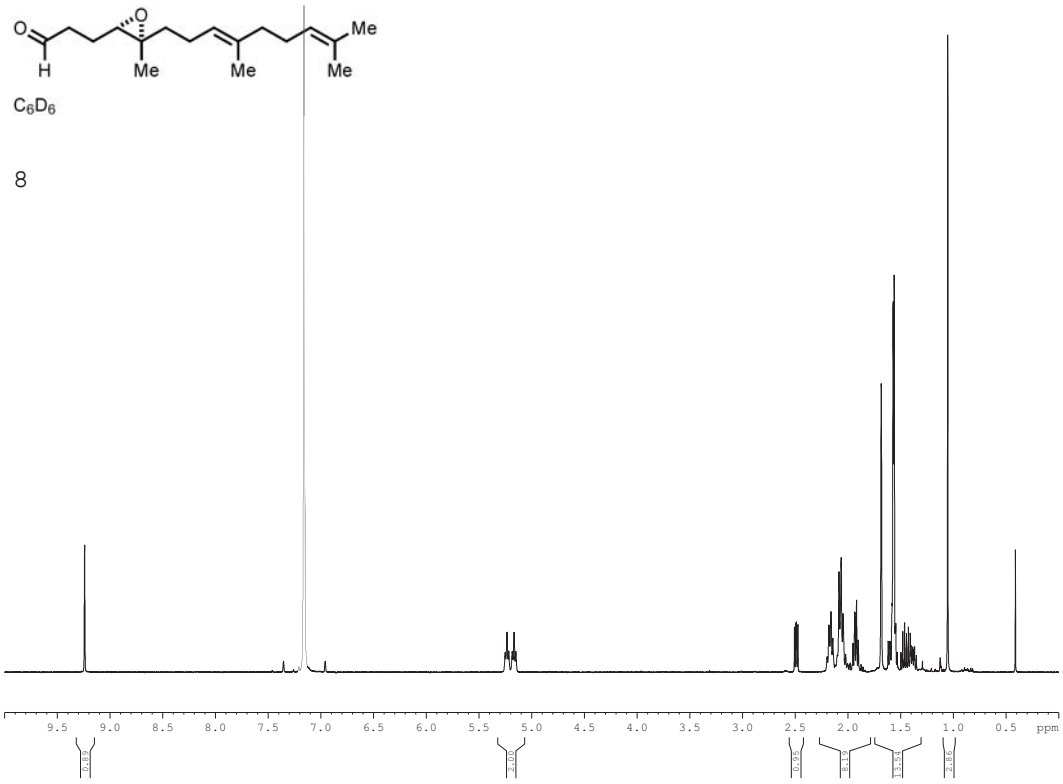
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C6D6
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2.00
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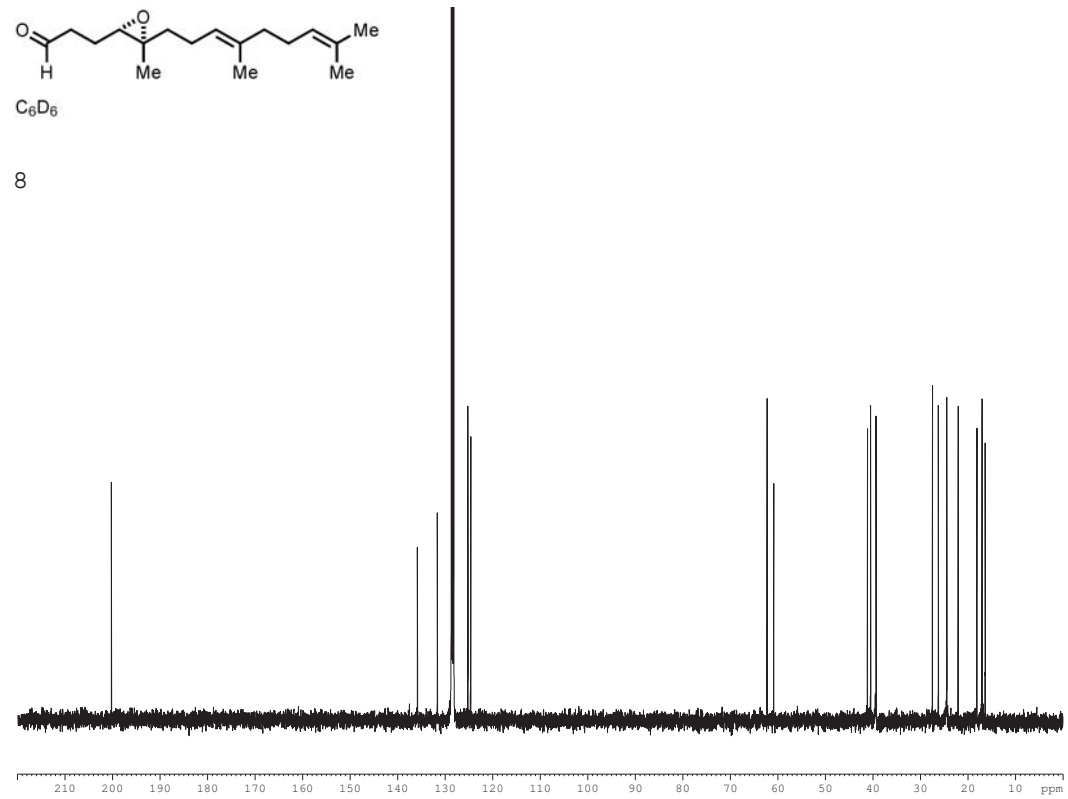
8.17
3.94
2.86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8
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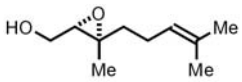

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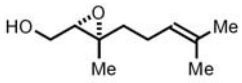

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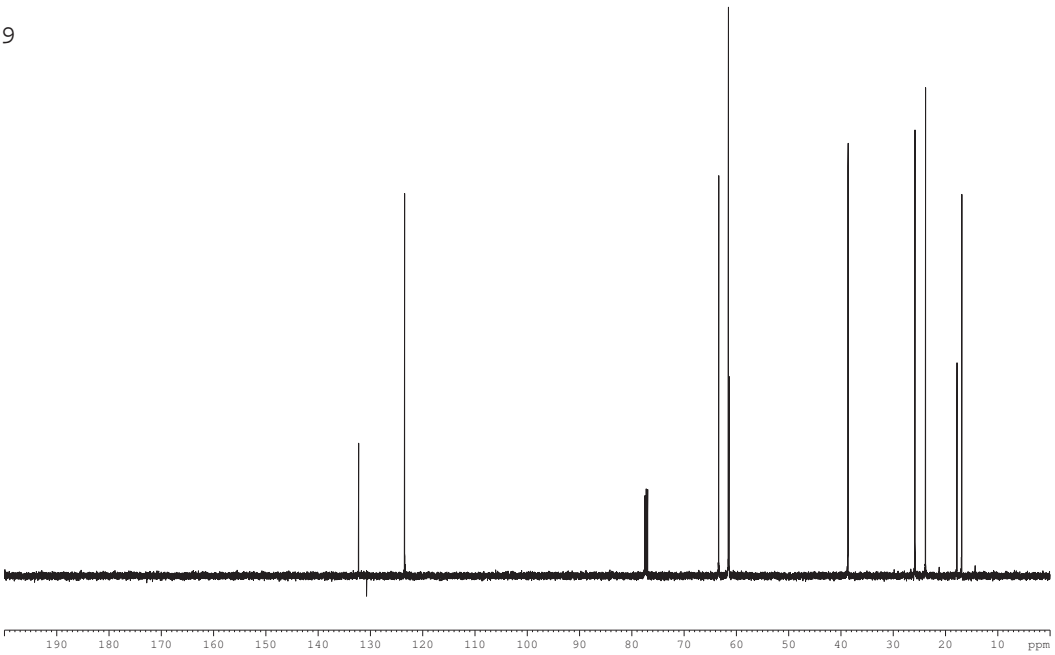

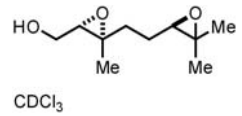

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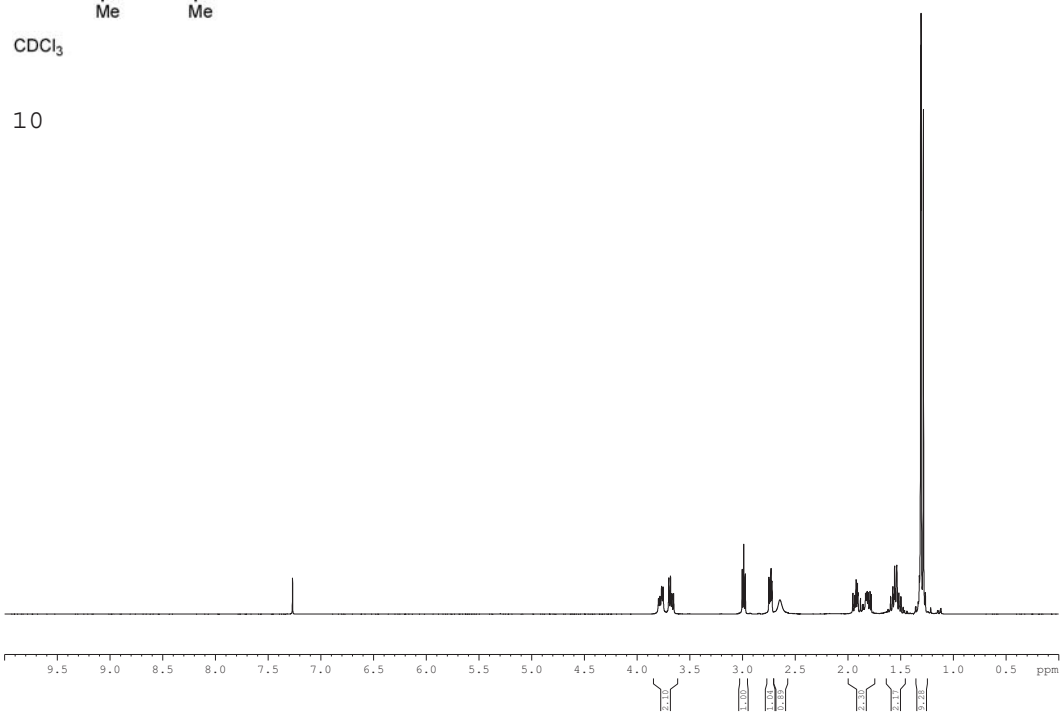

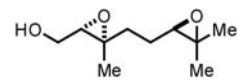

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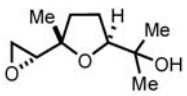

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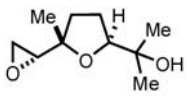

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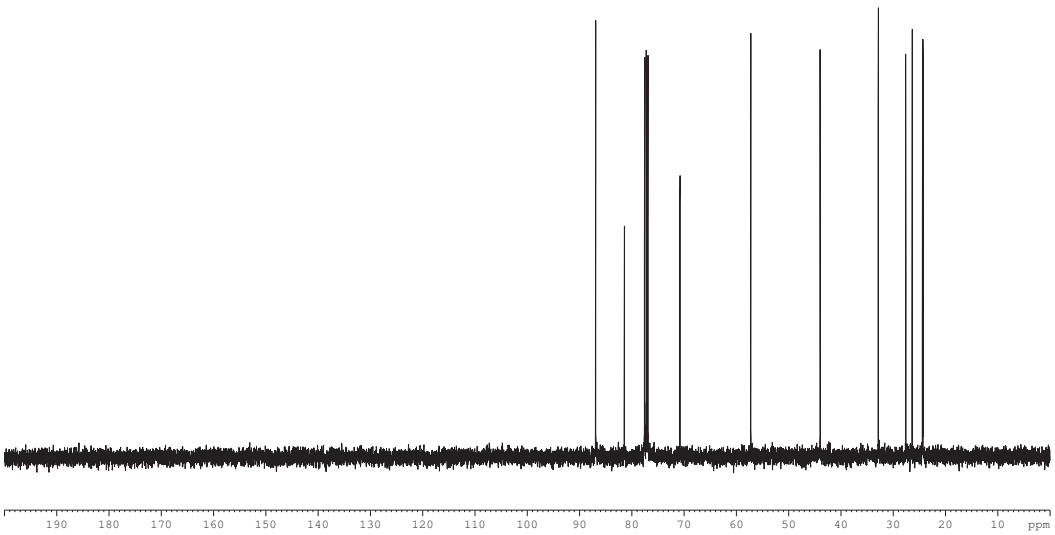

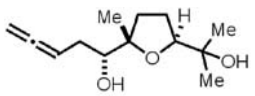

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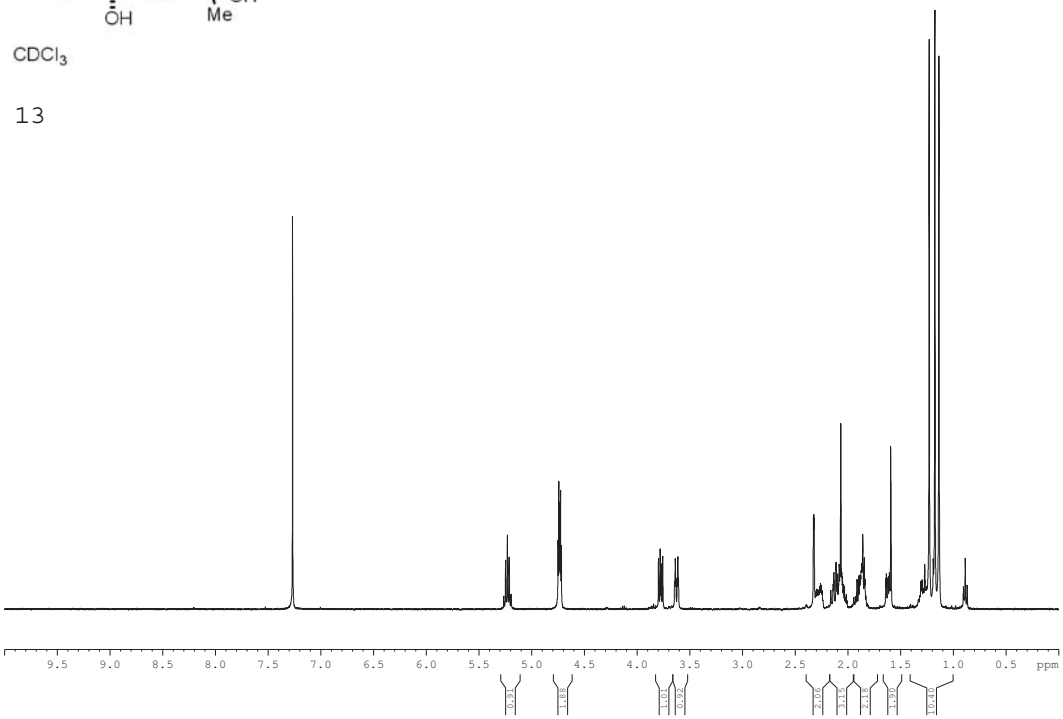

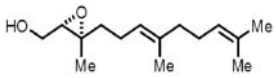

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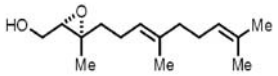

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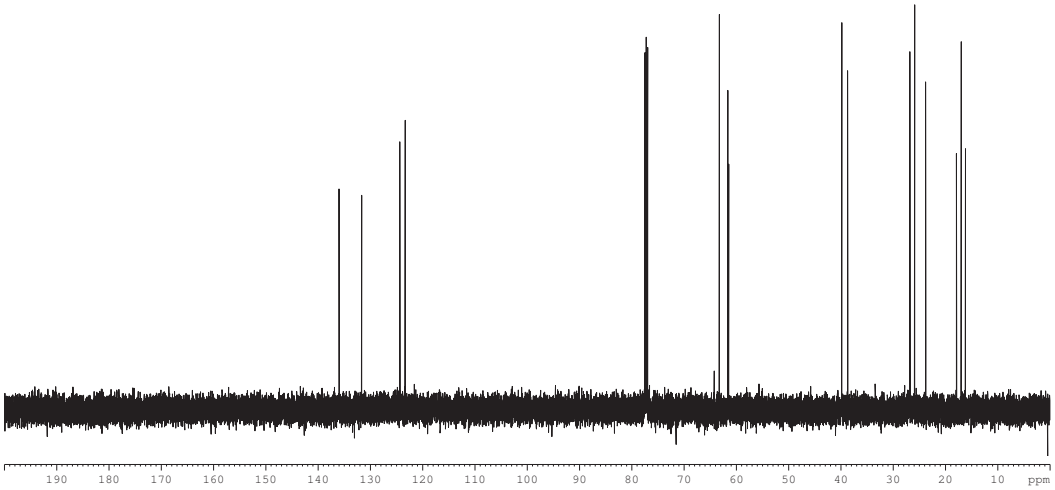
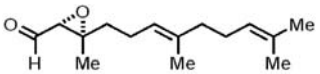
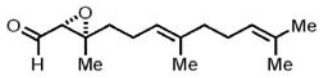




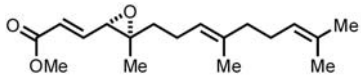
$CDCl_3$

16



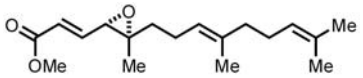
$CDCl_3$

16



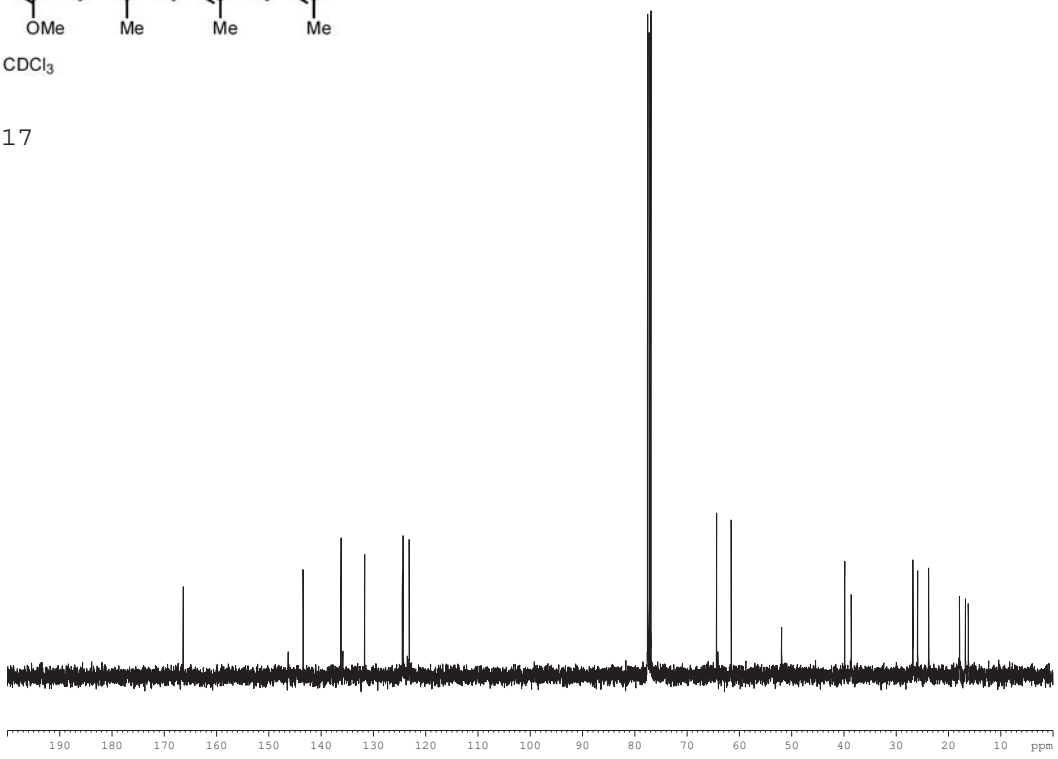
$CDCl_3$

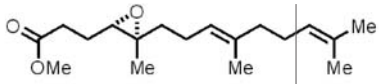
17



$CDCl_3$

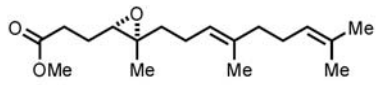
17





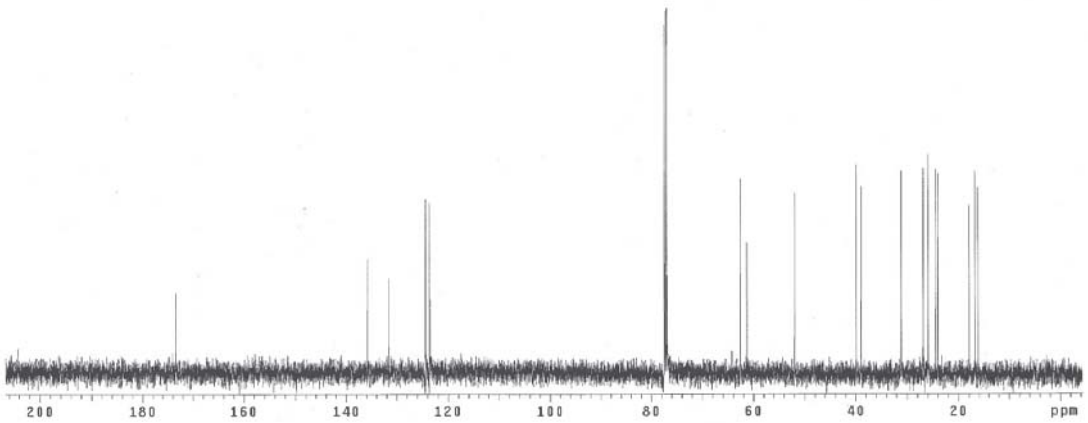
C_6D_6

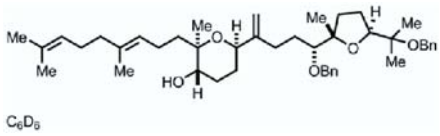
18



$CDCl_3$

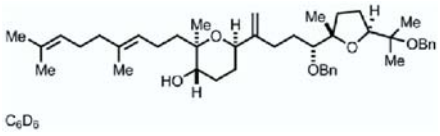
18





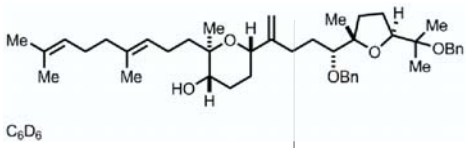
C_6D_6

(R)-20


Me
Me
Me
Me
O
H
HO
H
Me
H
O
Me
OBn
Me
OBn
C6D6

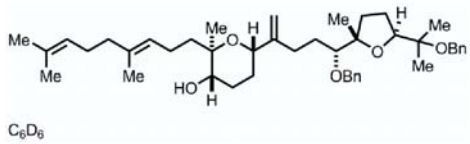
(R)-20

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Me
Me
Me
Me
O
H
HO
H
Me
H
O
Me
OBn
Me
OBn
C6D6

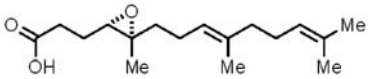
(S)-20

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.08
1.03
1.00
1.76
1.05
2.00
1.02
2.05
2.01
1.00
0.98
0.89
8.40
10.00
7.08
1.34
15.00

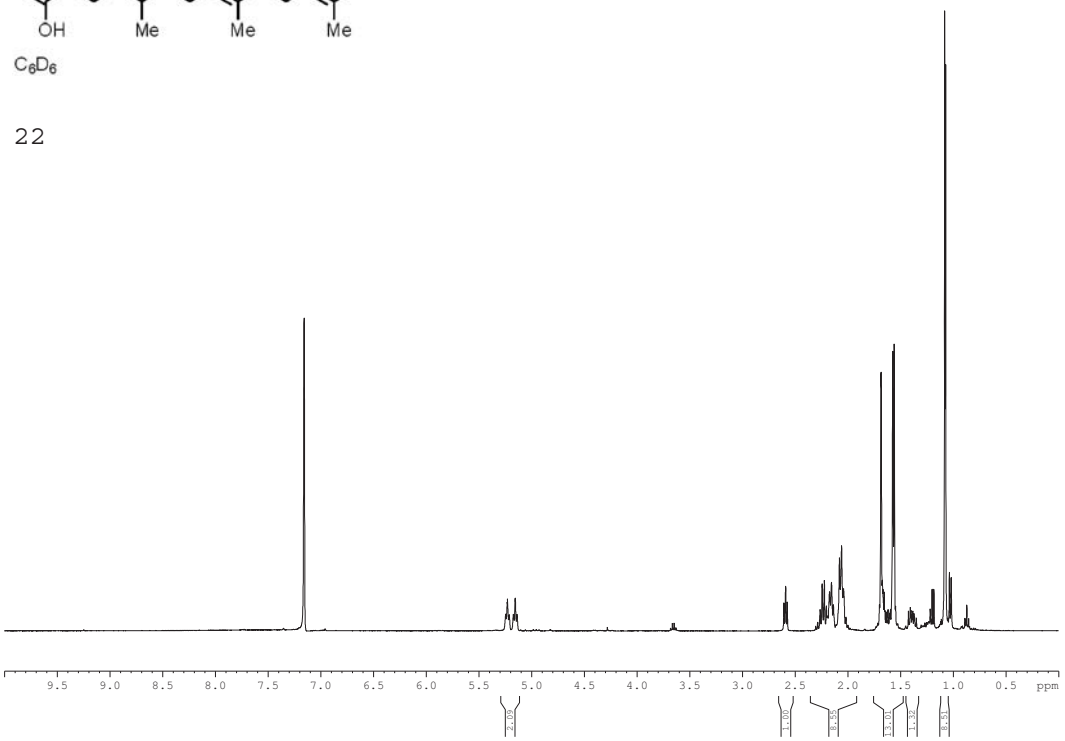

Me
Me
Me
Me
O
H
HO
H
Me
H
O
Me
OBn
OBn
Me
C6D6

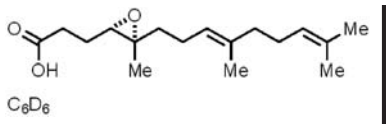
(S)-20

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
OH
O
Me
Me
Me
C6D6

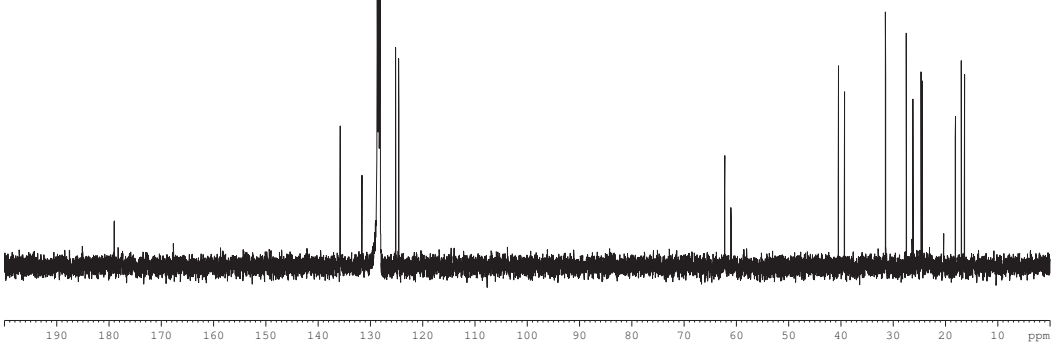
22

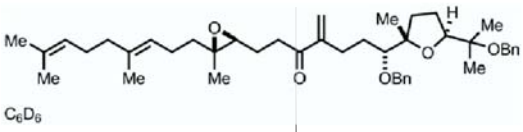

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
1.00
8.25
13.01
1.02
8.51



C_6D_6

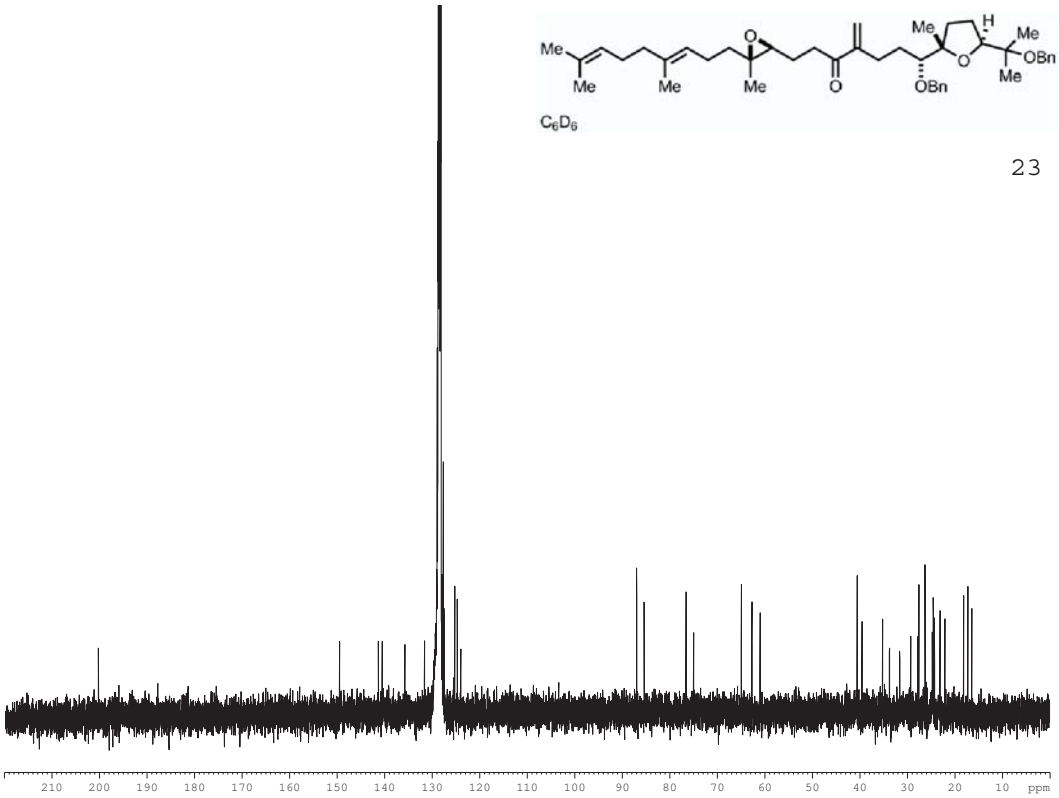
22



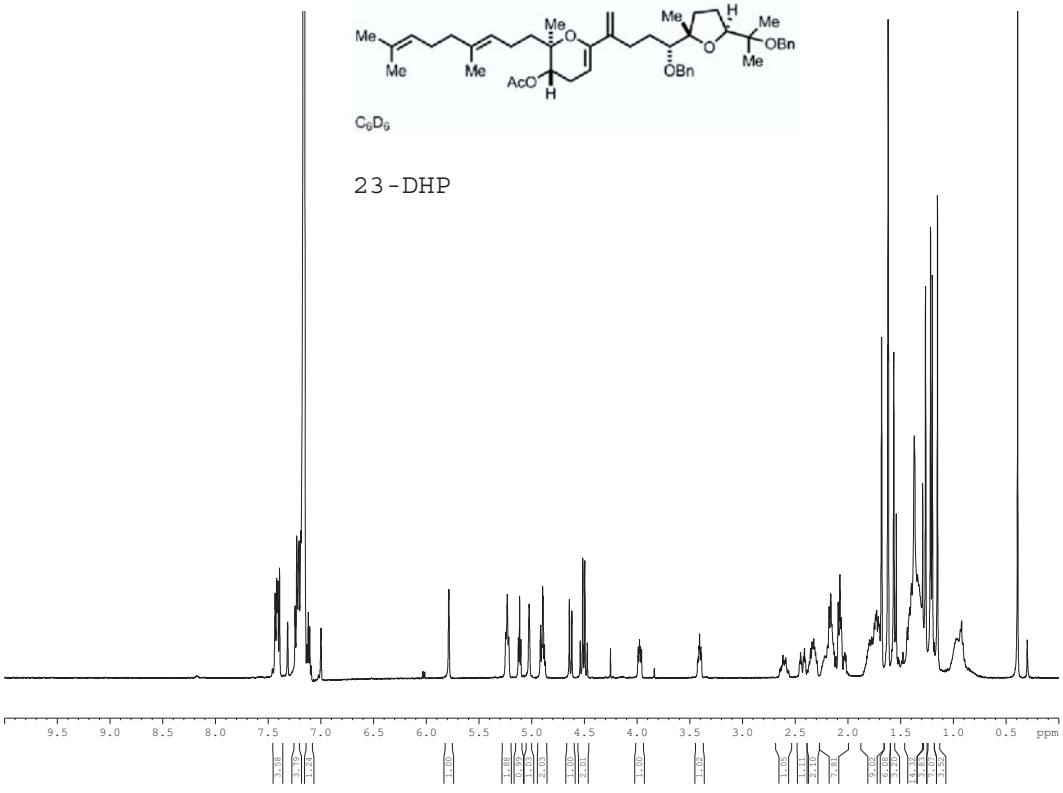


C_6D_6

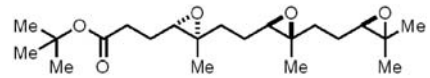
23


Me
Me
Me
Me
O
O
Me
H
O
Me
OBn
Me
OBn
C6D6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

23

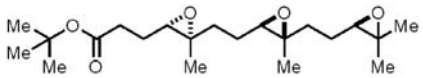

Me
Me
Me
Me
O
AcO
H
Me
O
H
Me
OBn
Me
OBn
C6D6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

23-DHP



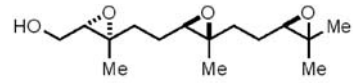
C_6D_6

29



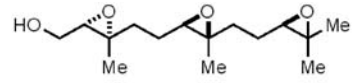
C_6D_6

29



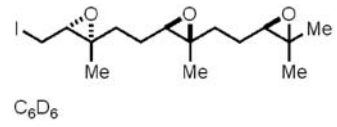
$CDCl_3$

30



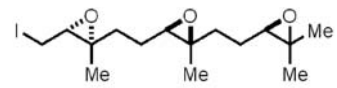
$CDCl_3$

30



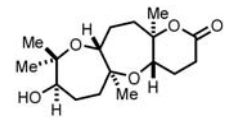
C_6D_6

30-iodide



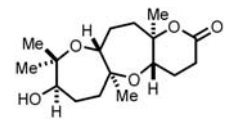
C_6D_6

30-iodide



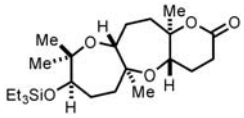
C_6D_6

31



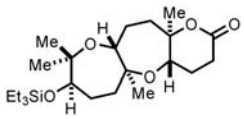
C_6D_6

31



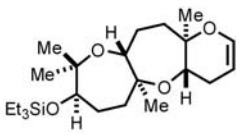
C_6D_6

32



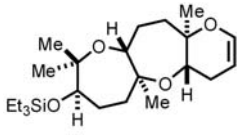
C_6D_6

32



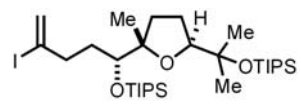
C_6D_6

32-enol ether



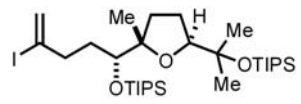
C_6D_6

32-enol ether



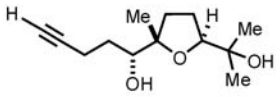
C_6D_6

35



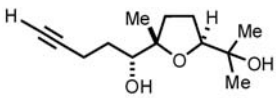
C_6D_6

35



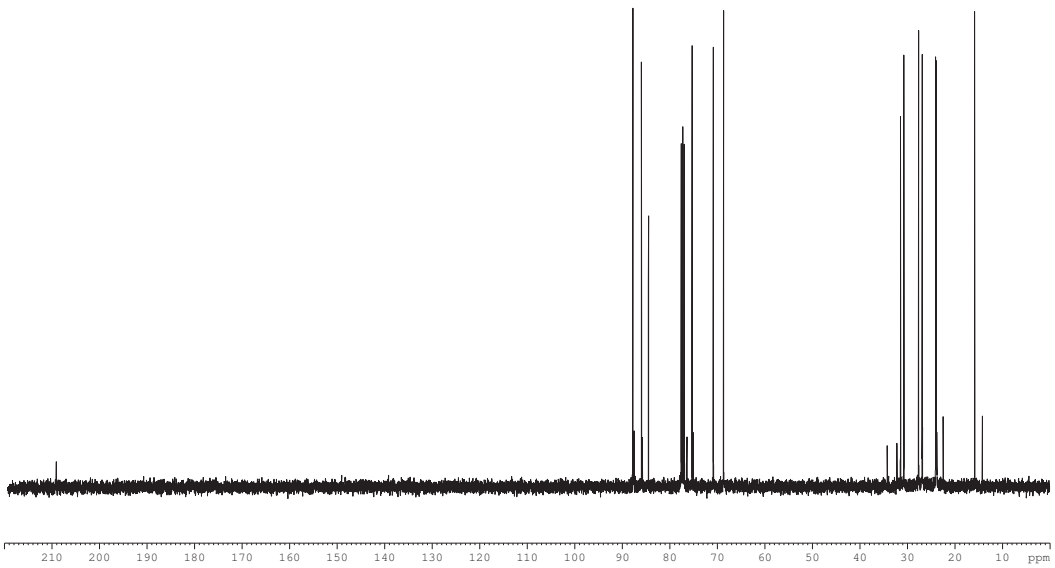
$CDCl_3$

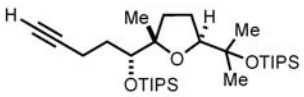
36



$CDCl_3$

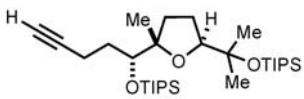
36





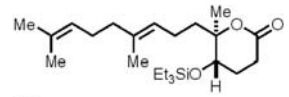
$CDCl_3$

37



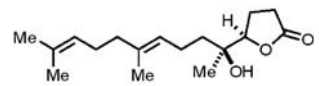
$CDCl_3$

37



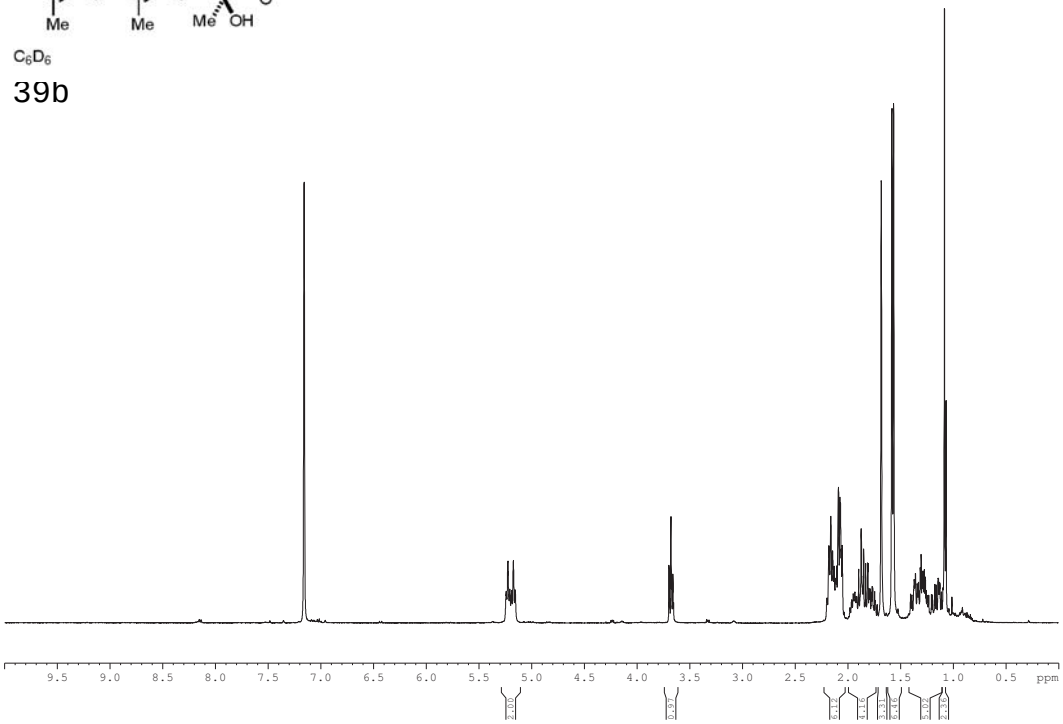
C_6D_6

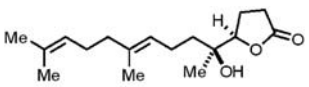
39



C_6D_6

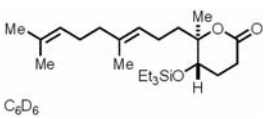
39b





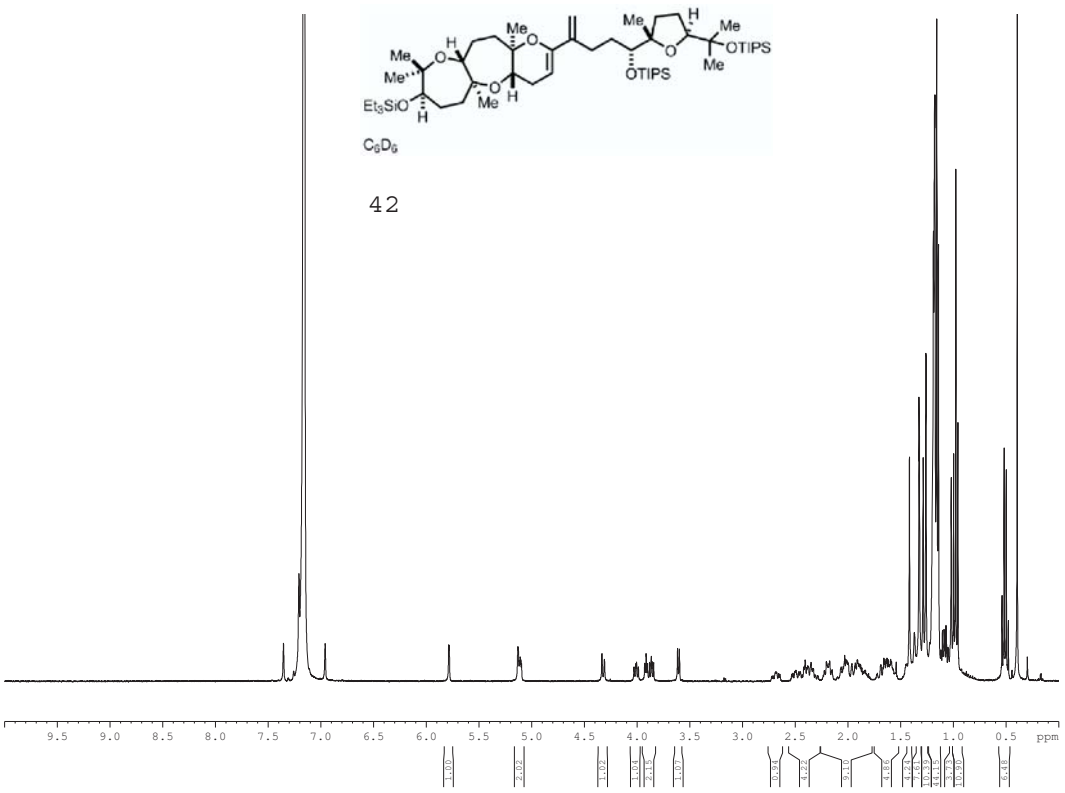
C_6D_6

39b

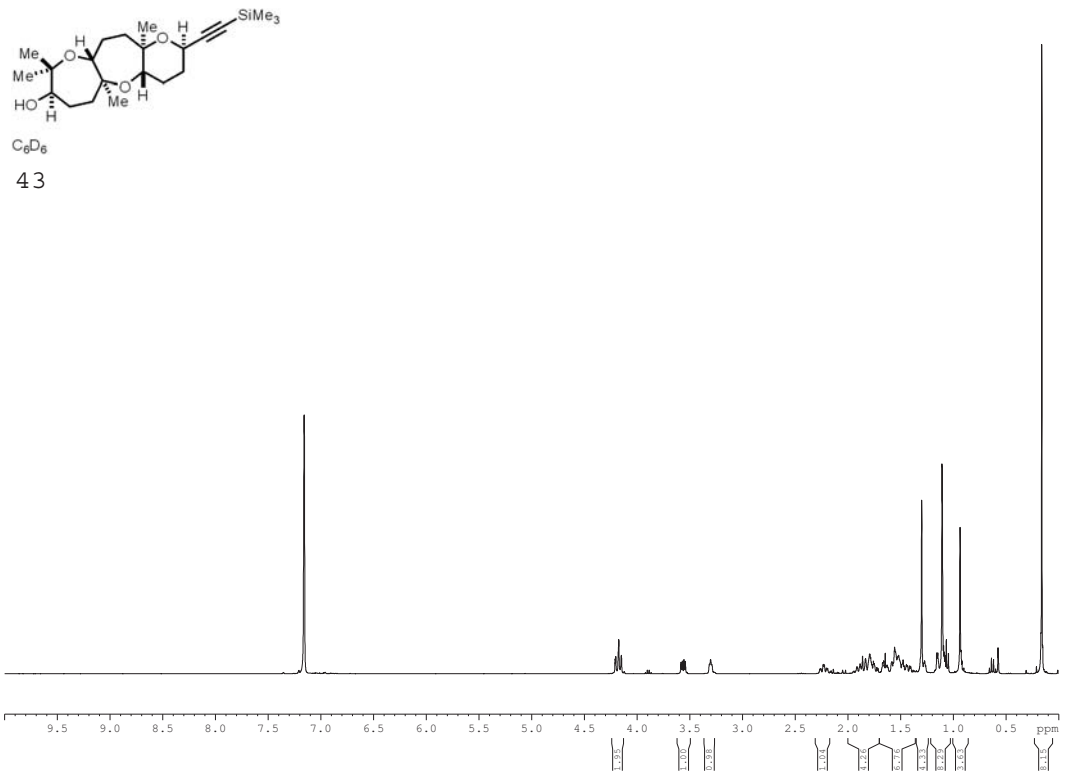


C_6D_6

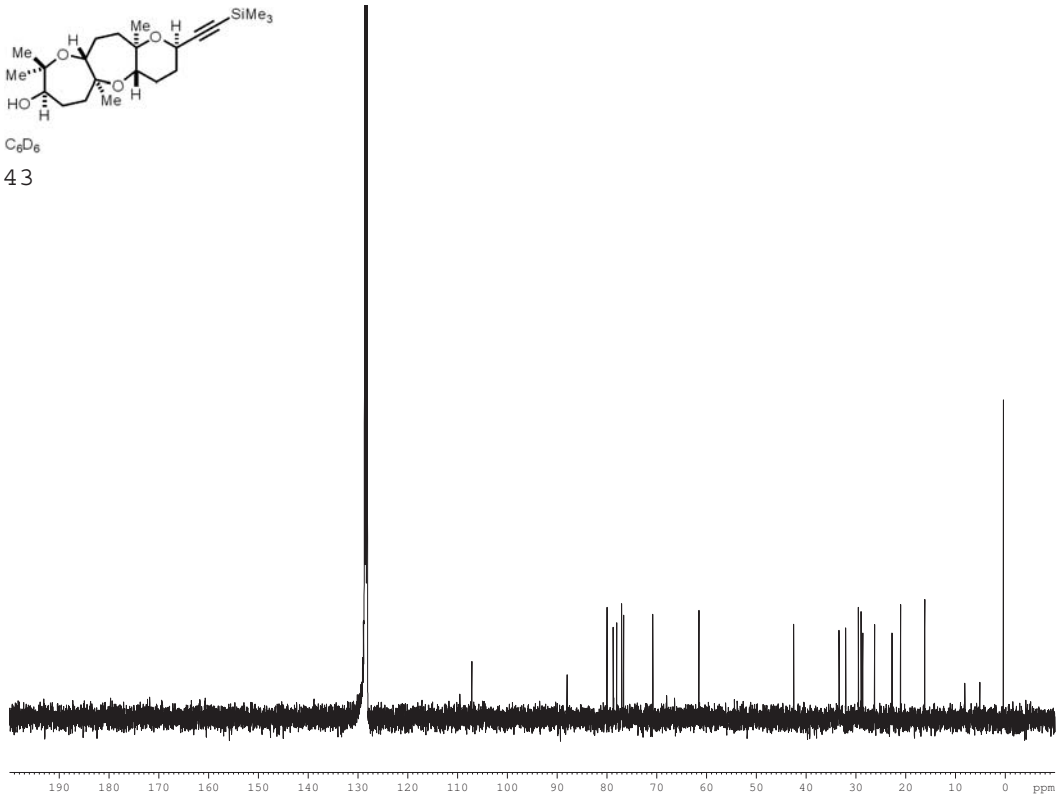
39

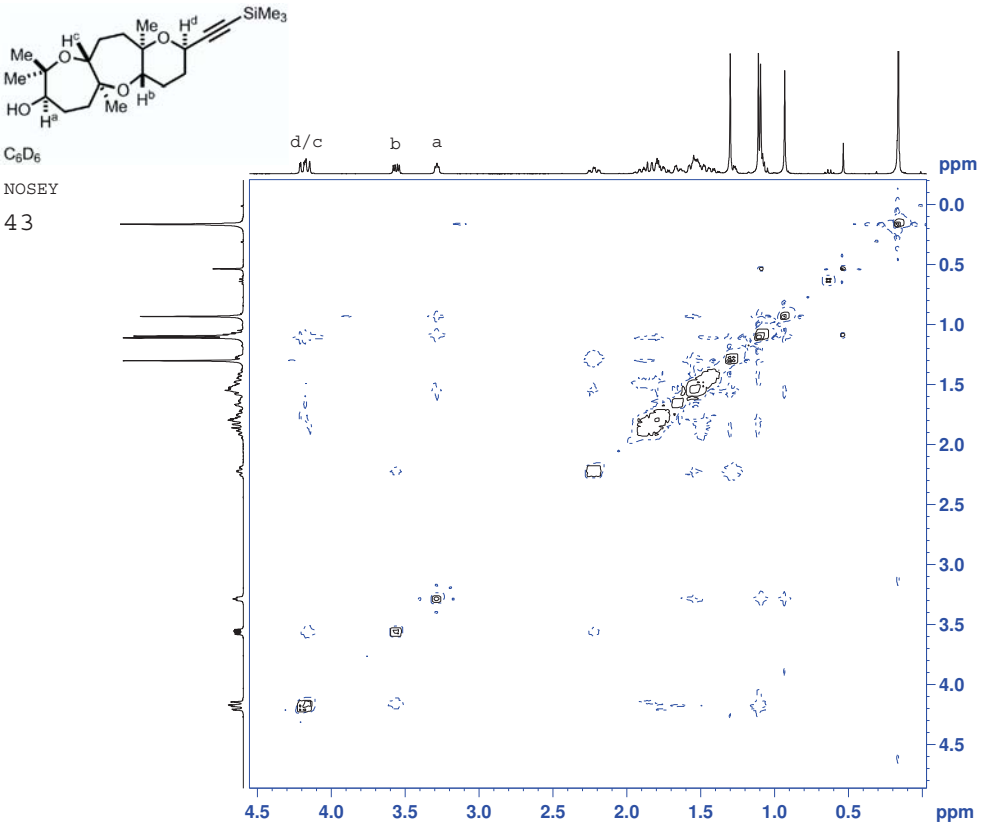

Me
Me
Me
H
Me
Me
OTIPS
Me
Me
OTIPS
Et3SiO
H
Me
H
C6D6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

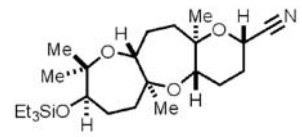
42


SiMe3
Me
H
Me
Me
O
H
HO
Me
H
C6D6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

43

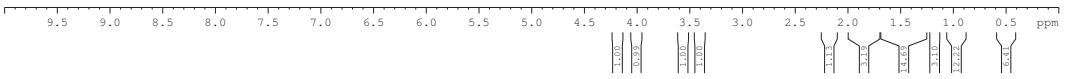

SiMe3
Me
Me
HO
H
O
Me
H
C6D6
43
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

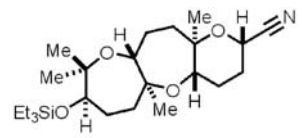

SiMe3
Hc
Hd
Hb
Ha
Me
HO
C6D6
NOSEY
43
d/c
b
a
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm



C_6D_6

44





C_6D_6

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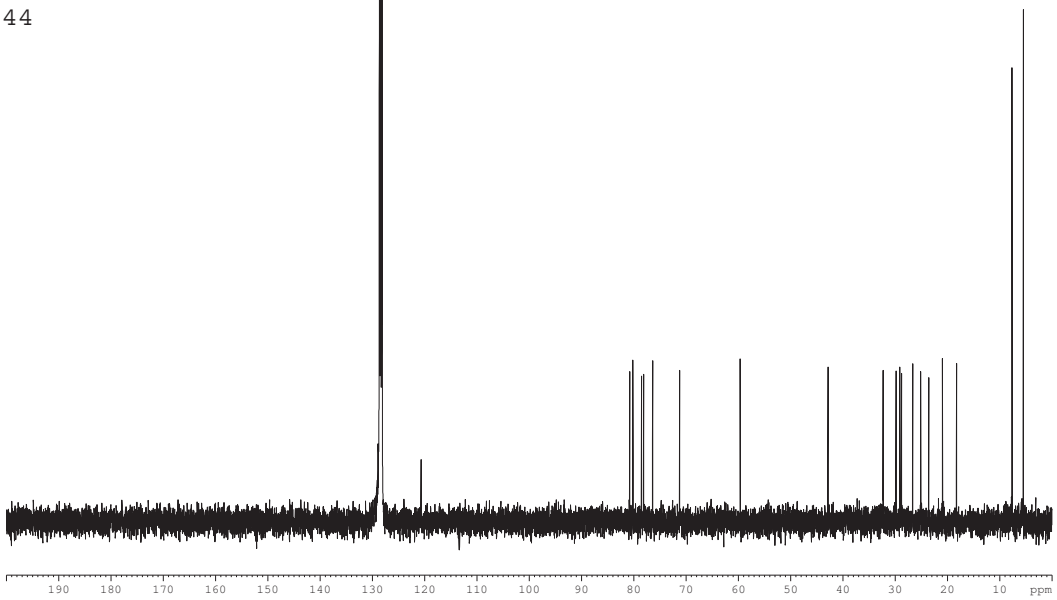

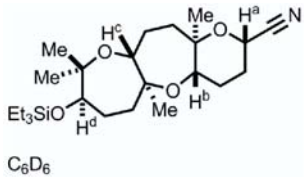

COSY

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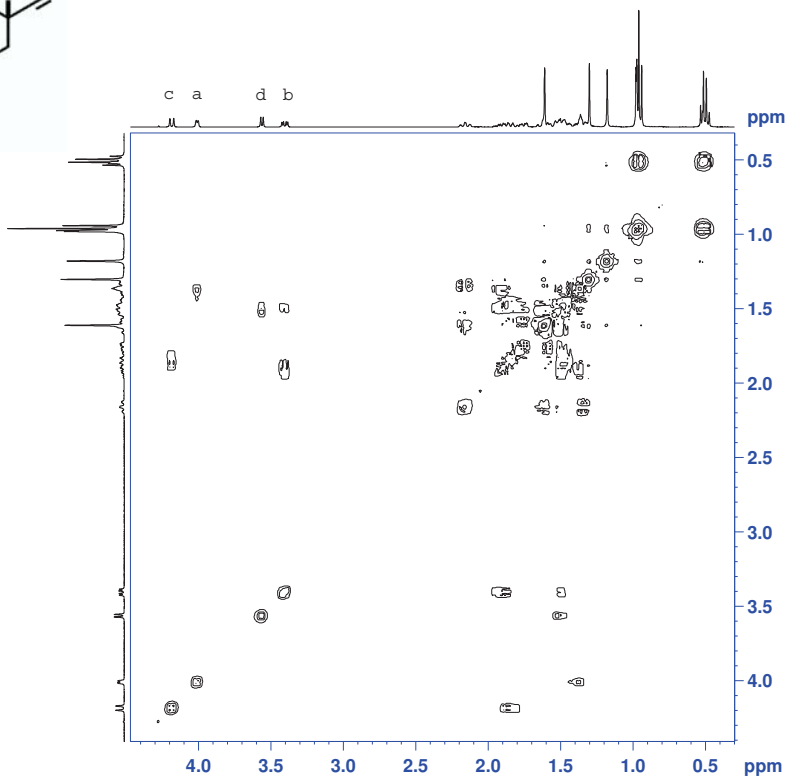

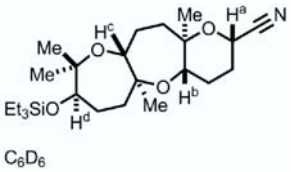

NOSEY

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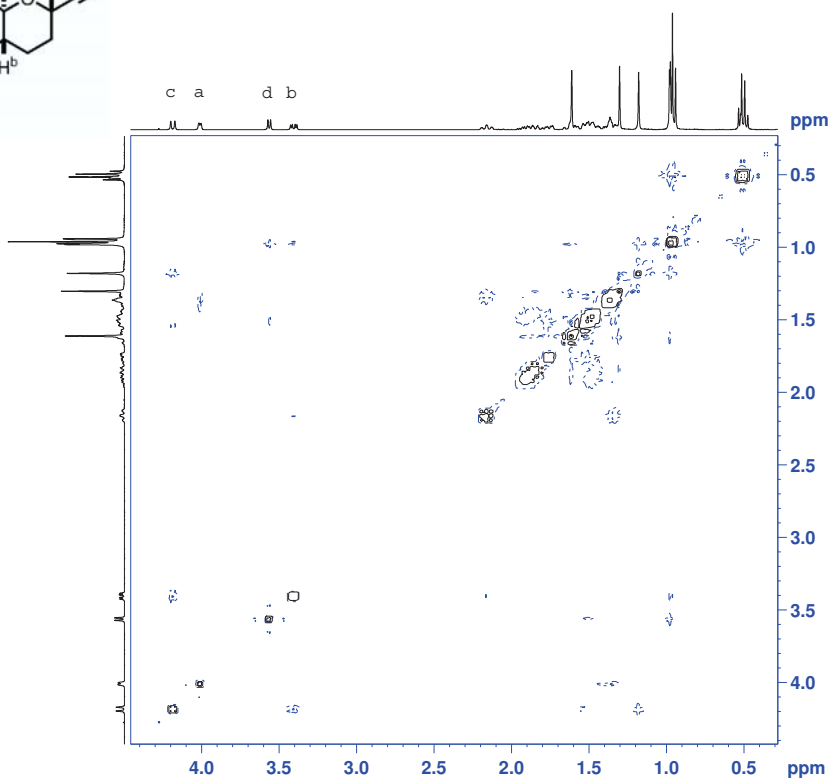
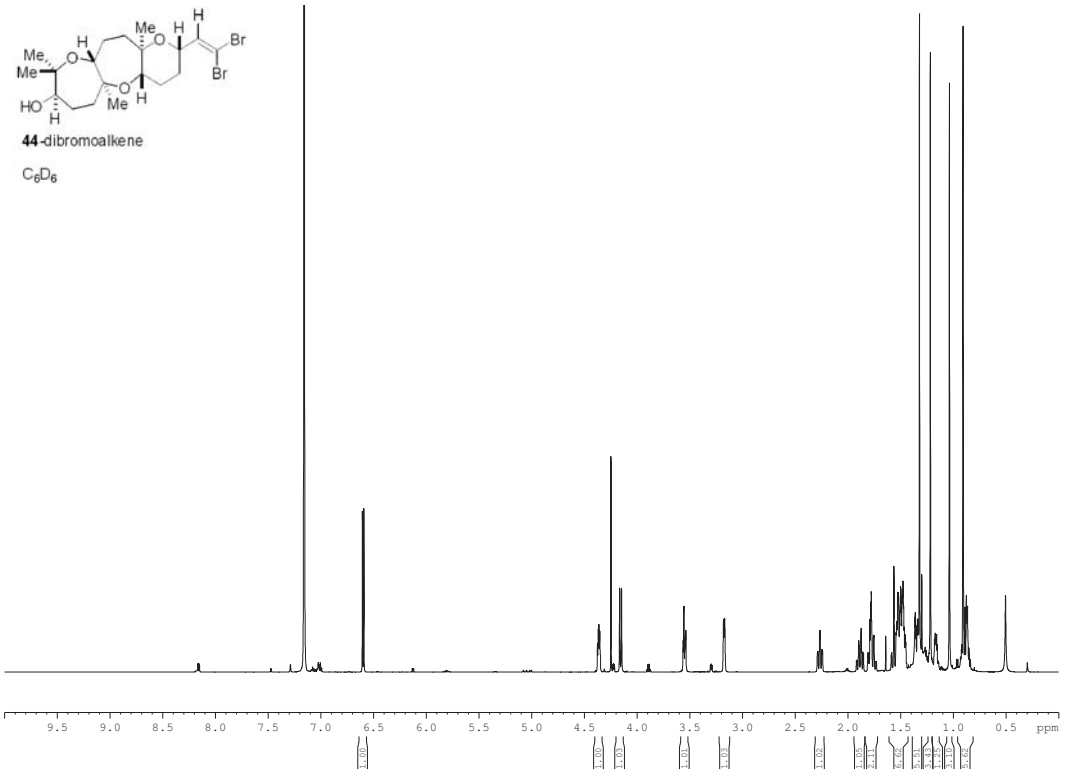
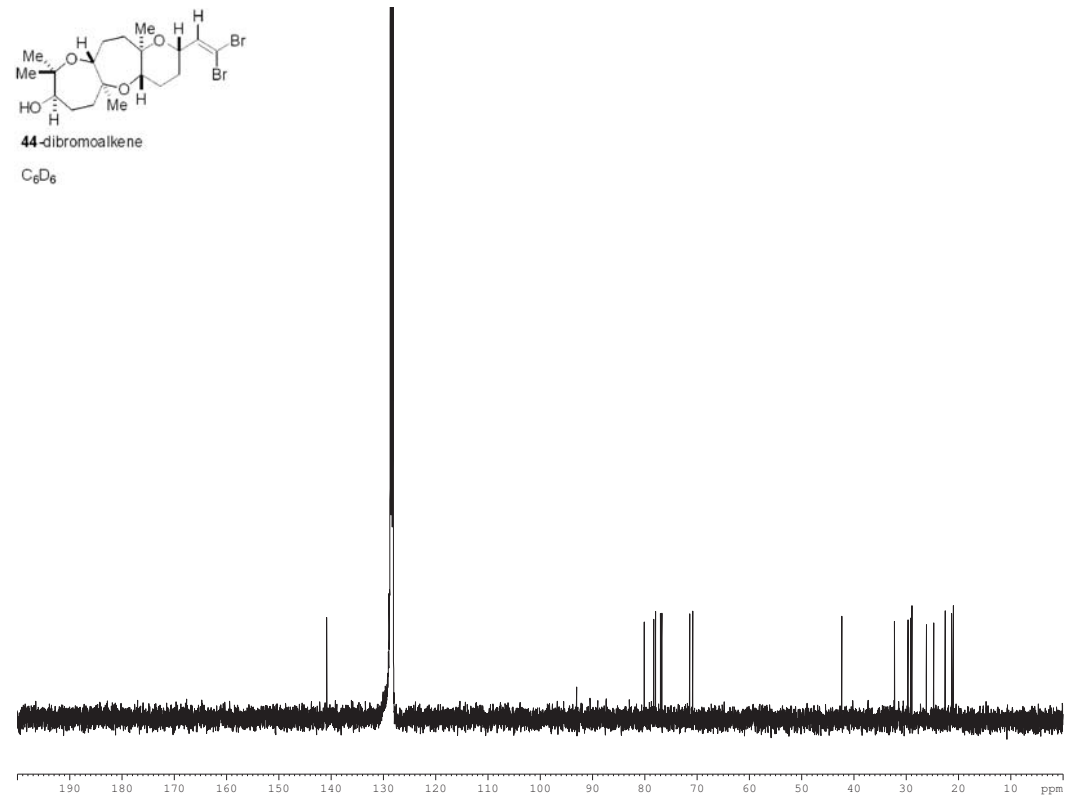
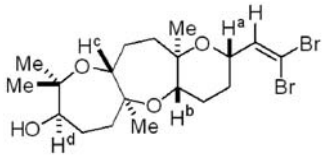



44-dibromoalkene
C6D6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

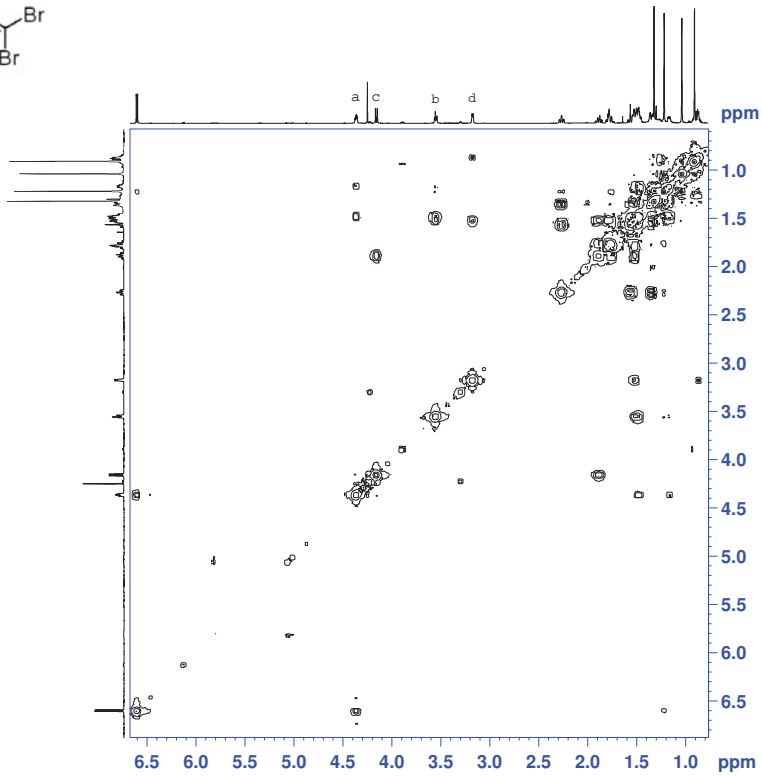

44-dibromoalkene
C6D6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

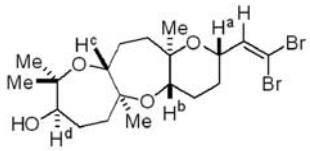


44-dibromoalkene

C_6D_6

COSY

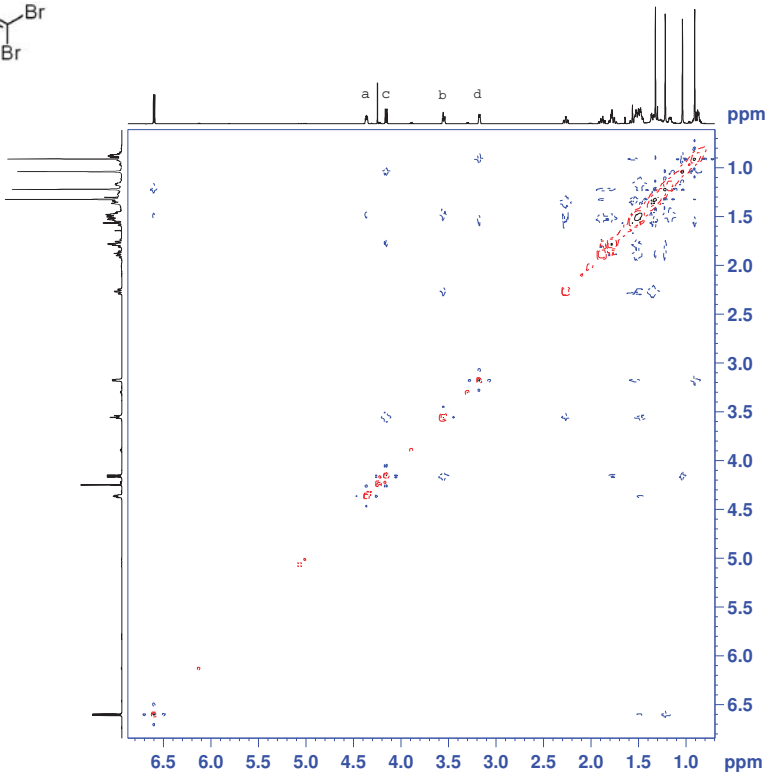


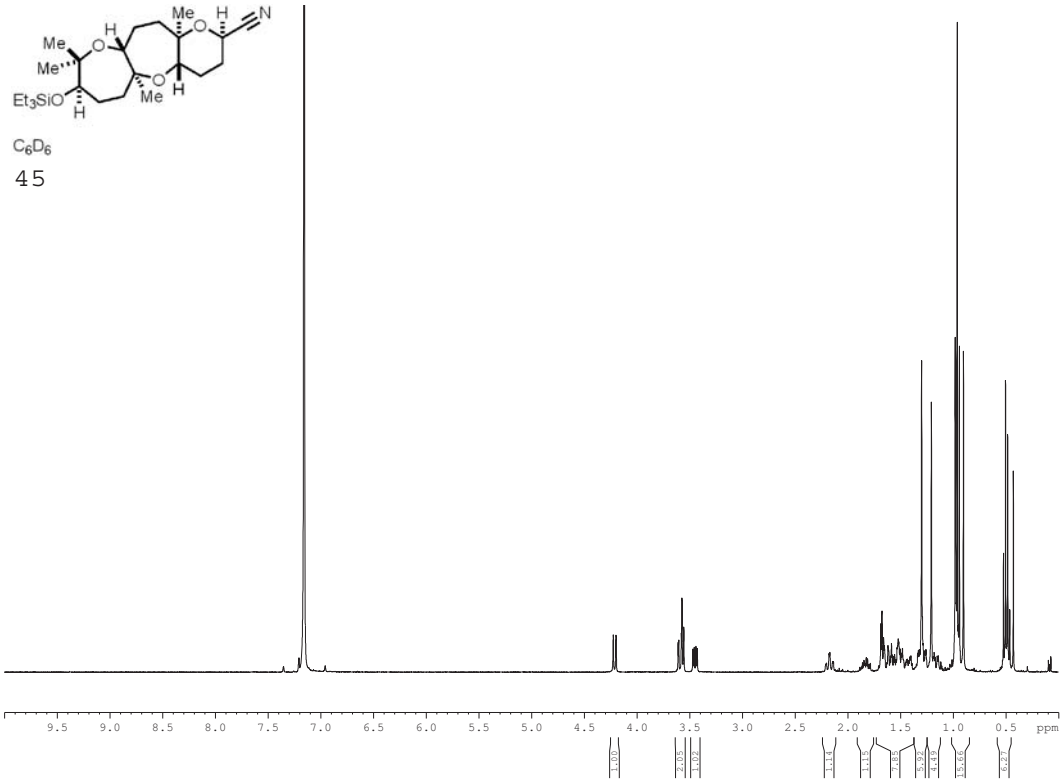


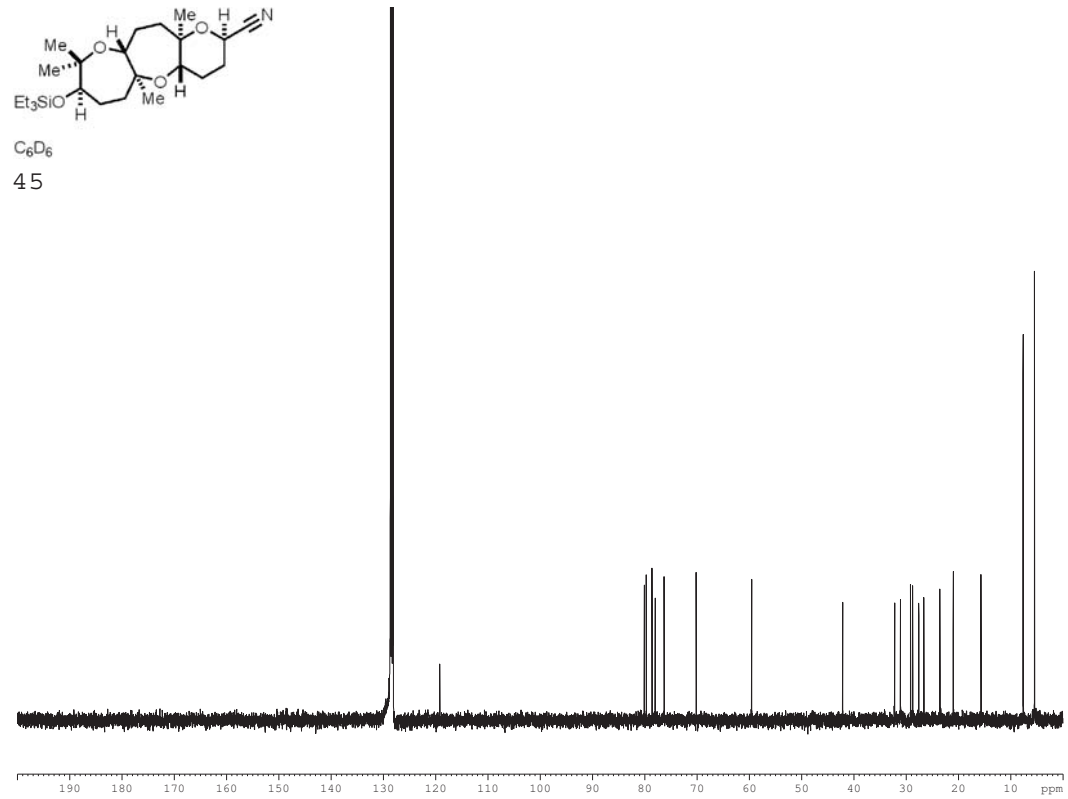
44-dibromoalkene

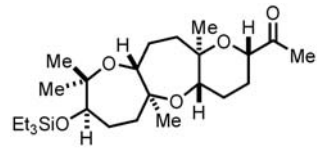
C_6D_6

NOSEY




Me
H
N
Me
Me
O
H
Et3SiO
H
O
Me
H
C6D6
45
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.05
1.02
1.14
1.16
2.86
5.02
4.49
15.66
6.27


Me
H
N
Me
Me
O
H
Et3SiO
H
O
Me
H
C6D6
45
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



C_6D_6

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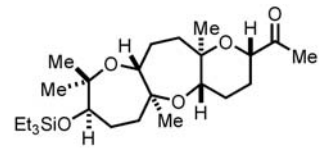

C_6D_6

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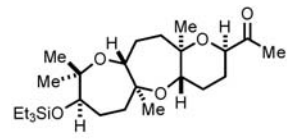

C_6D_6

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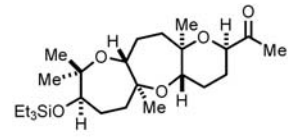
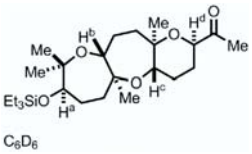


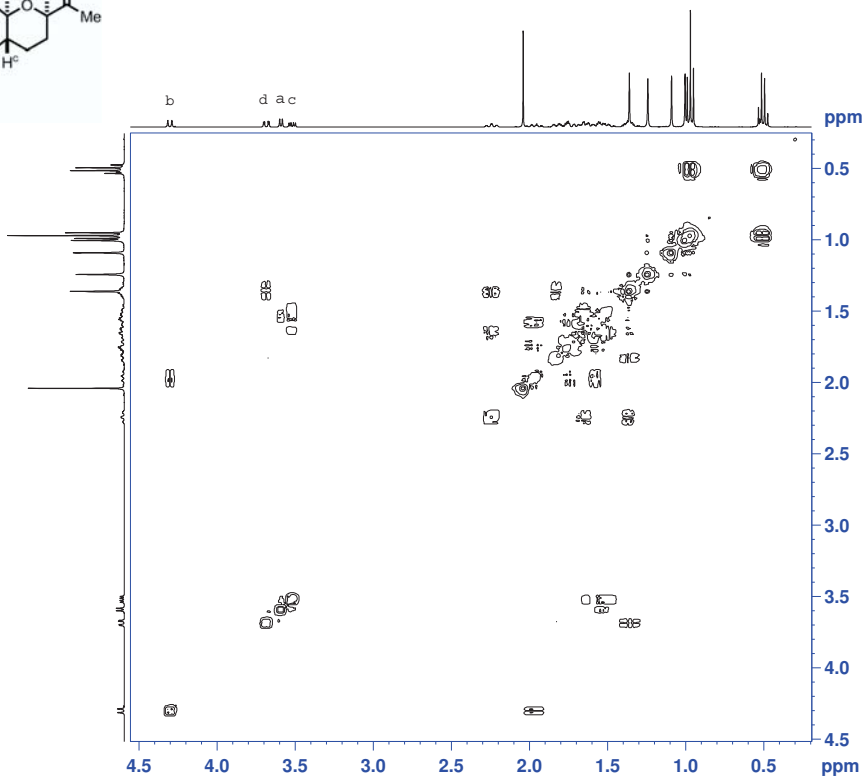
C_6D_6

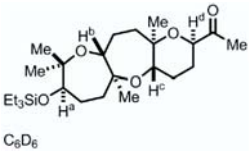
53



COSY

53





NOSEY

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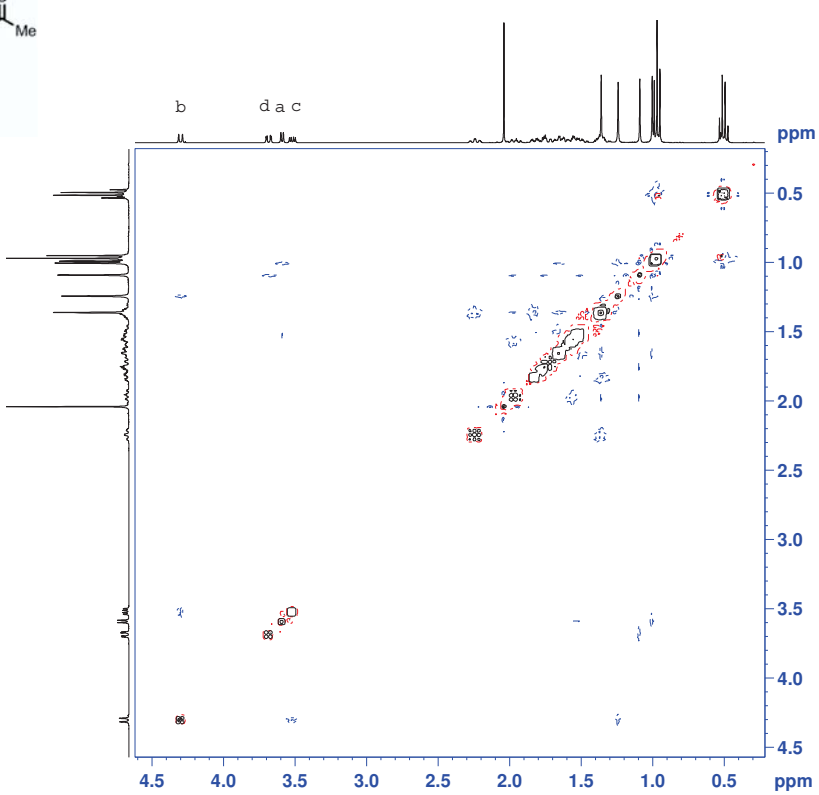

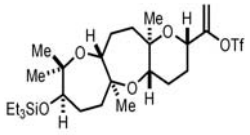

C_6D_6

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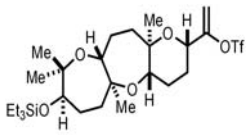

C_6D_6

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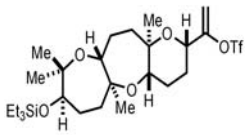

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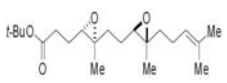

C_6D_6

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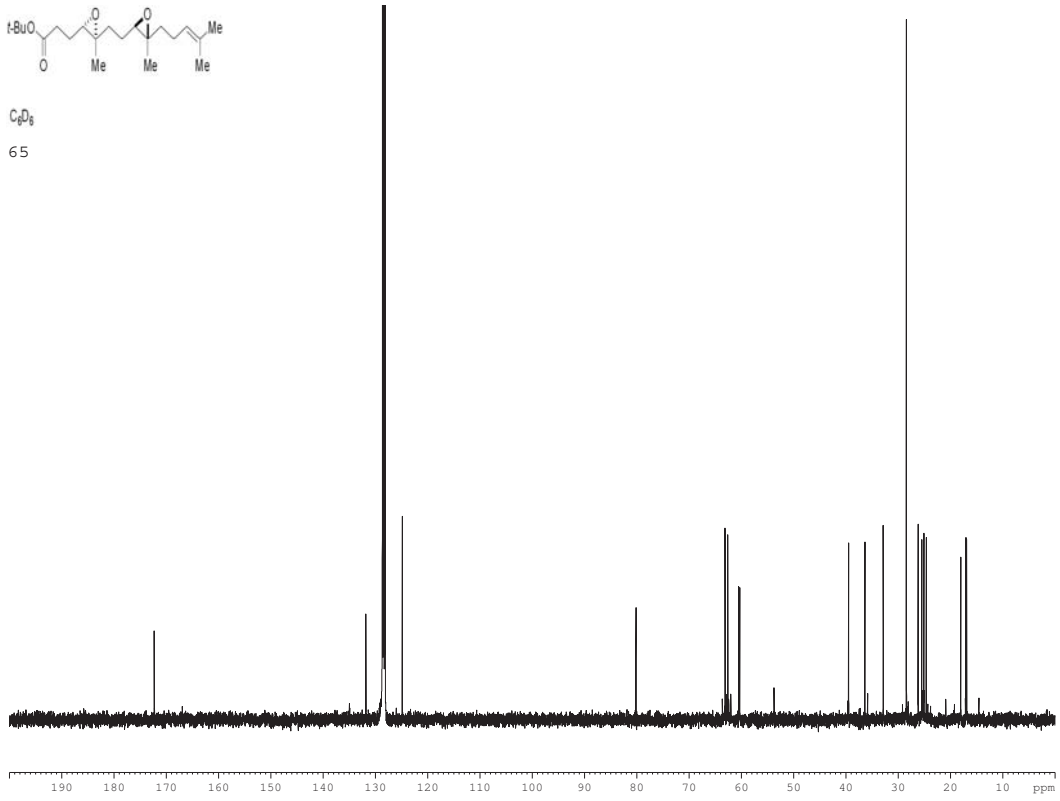
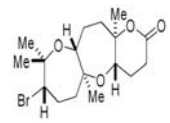

t-BuO
O
O
O
Me
Me
Me
Me
C6D6
65
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



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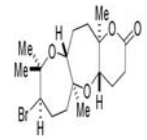
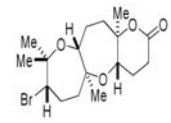


epi-66

C_6D_6



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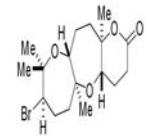

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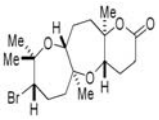

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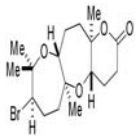
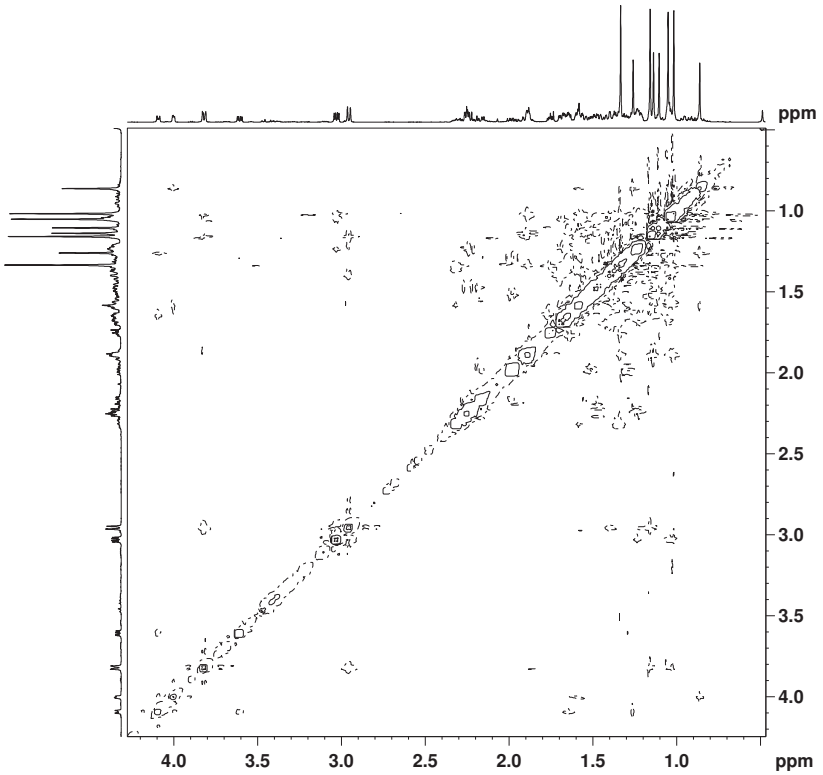
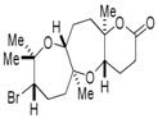


epi-66

C_6D_6

NOSEY





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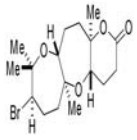

epi-66

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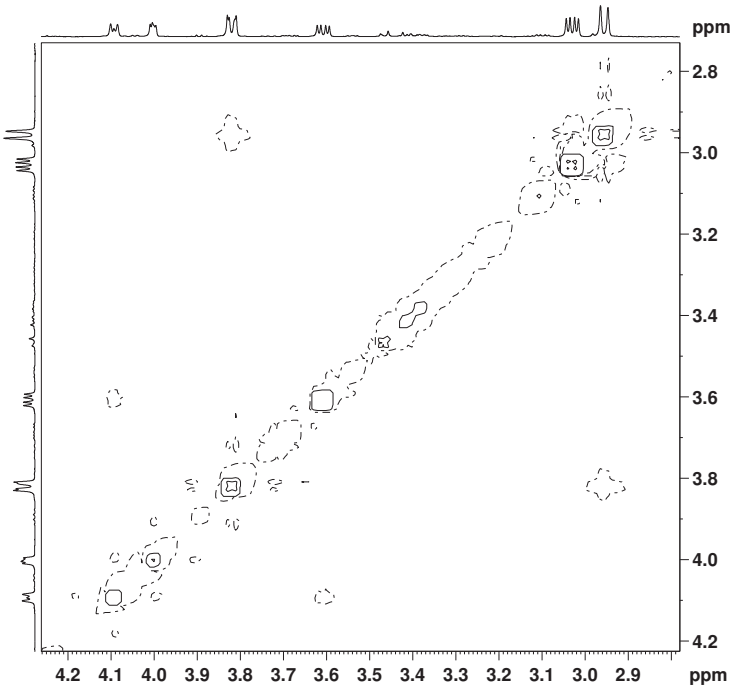

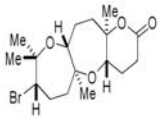

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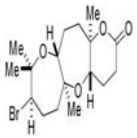
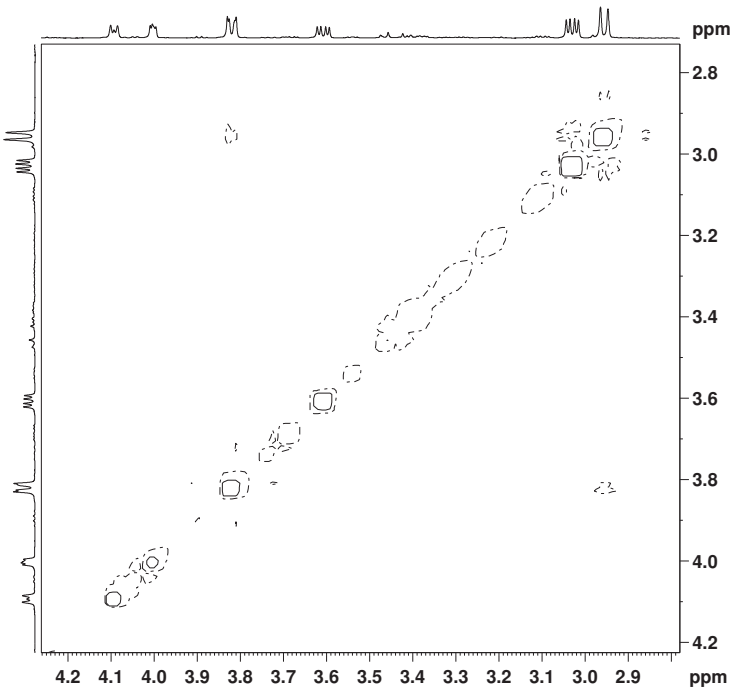
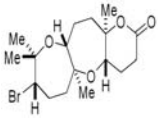


epi-66

C_6D_6

NOSEY





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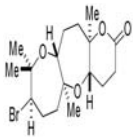
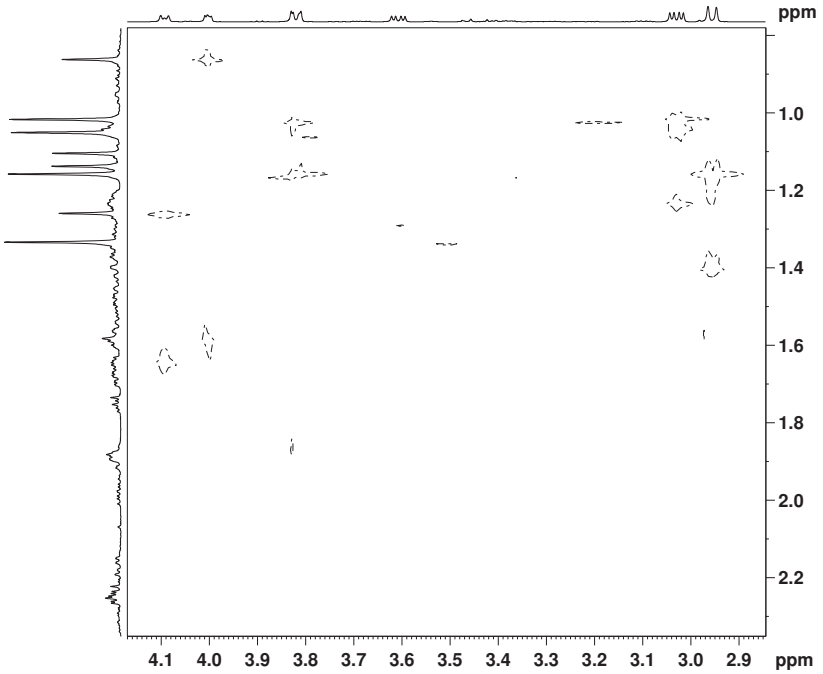
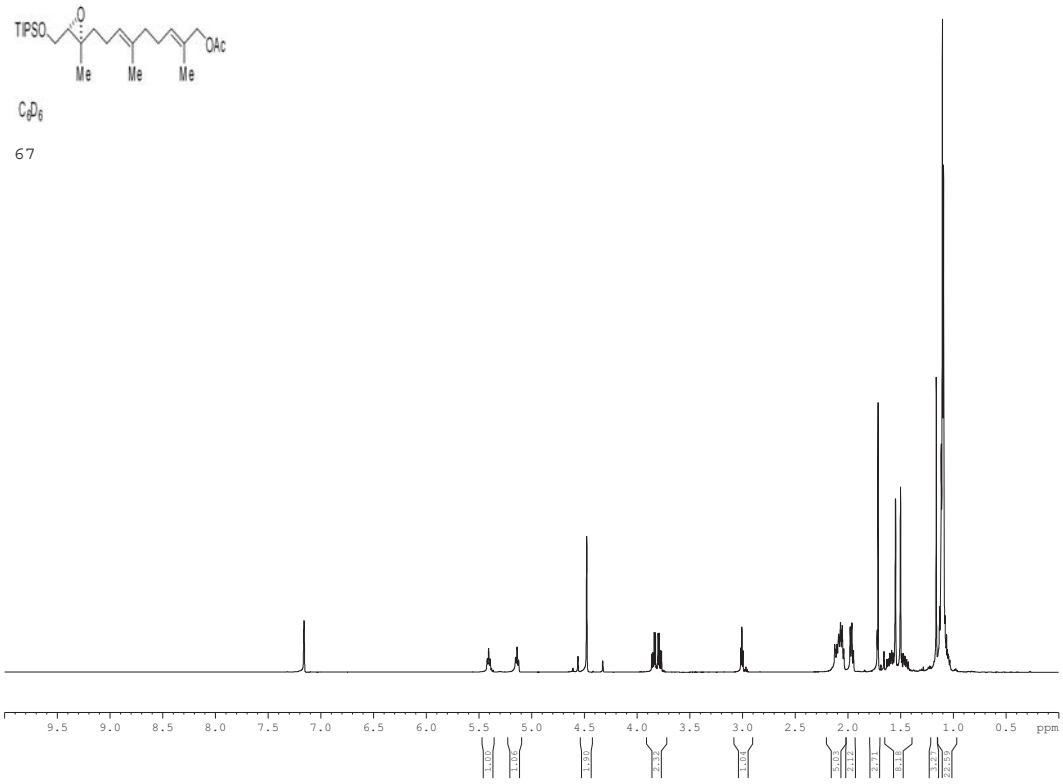


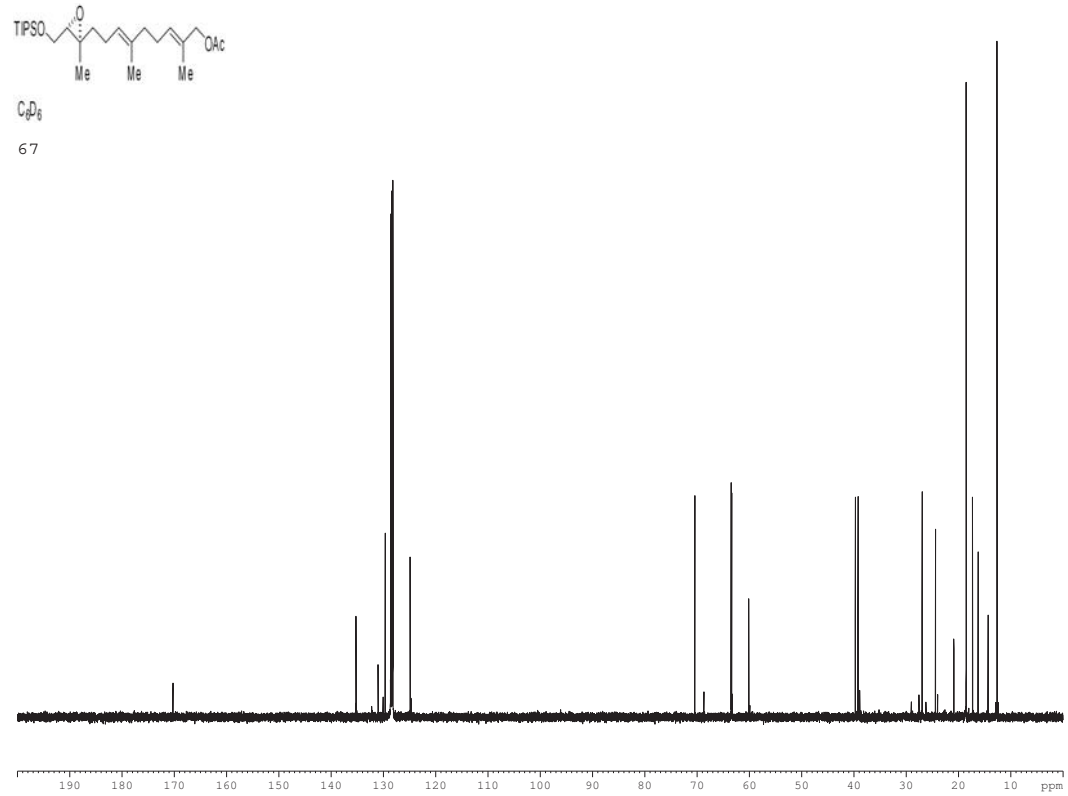
epi-66

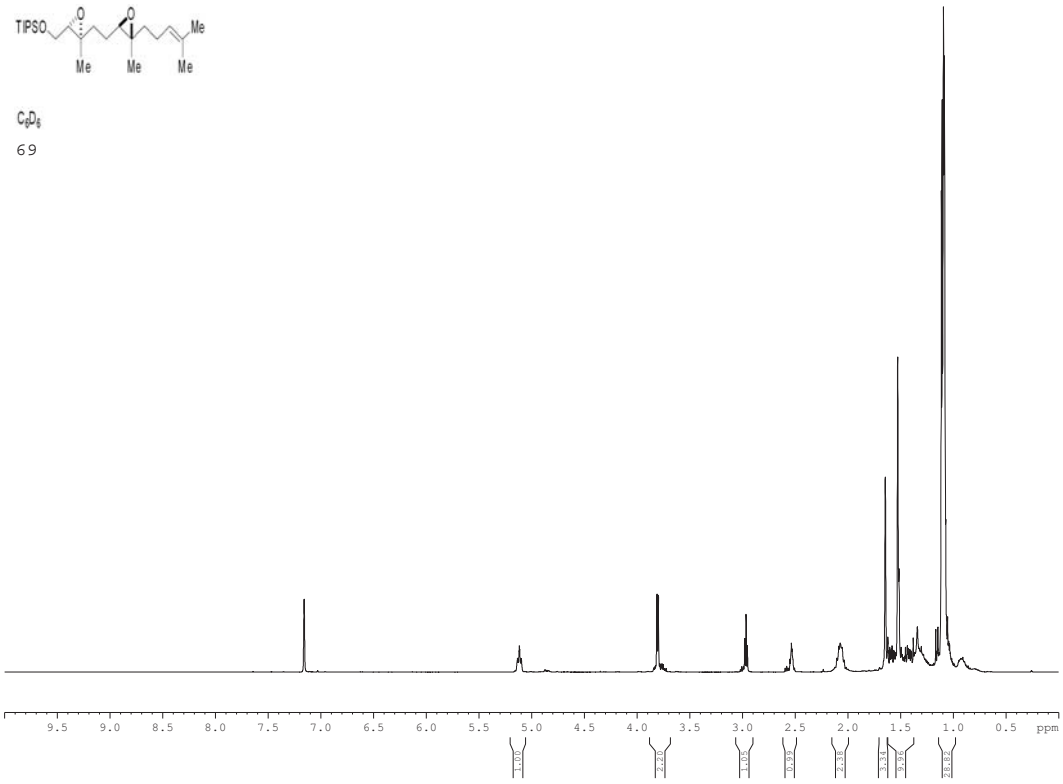
C_6D_6

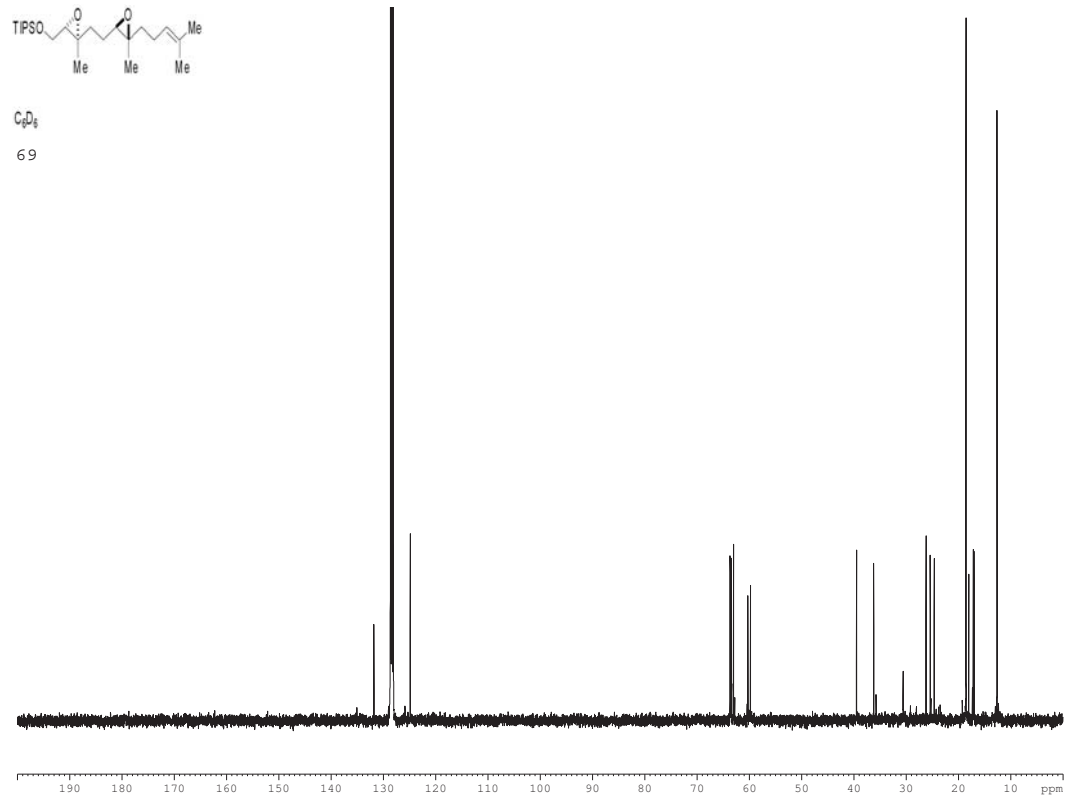
NOSEY

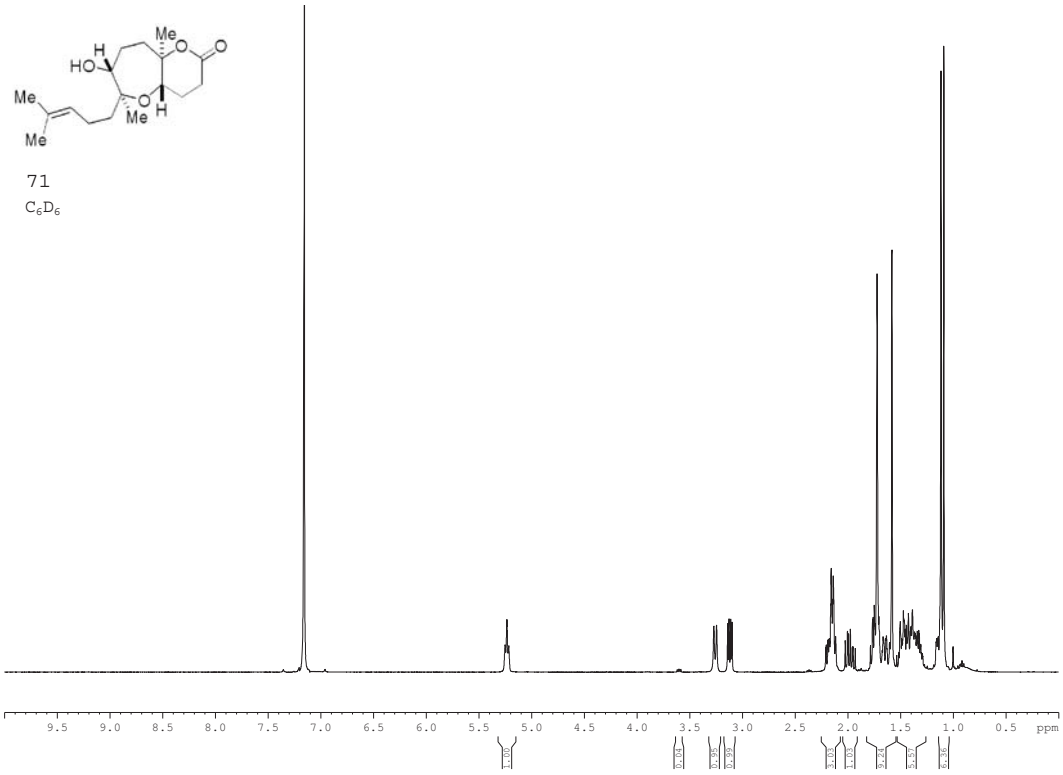


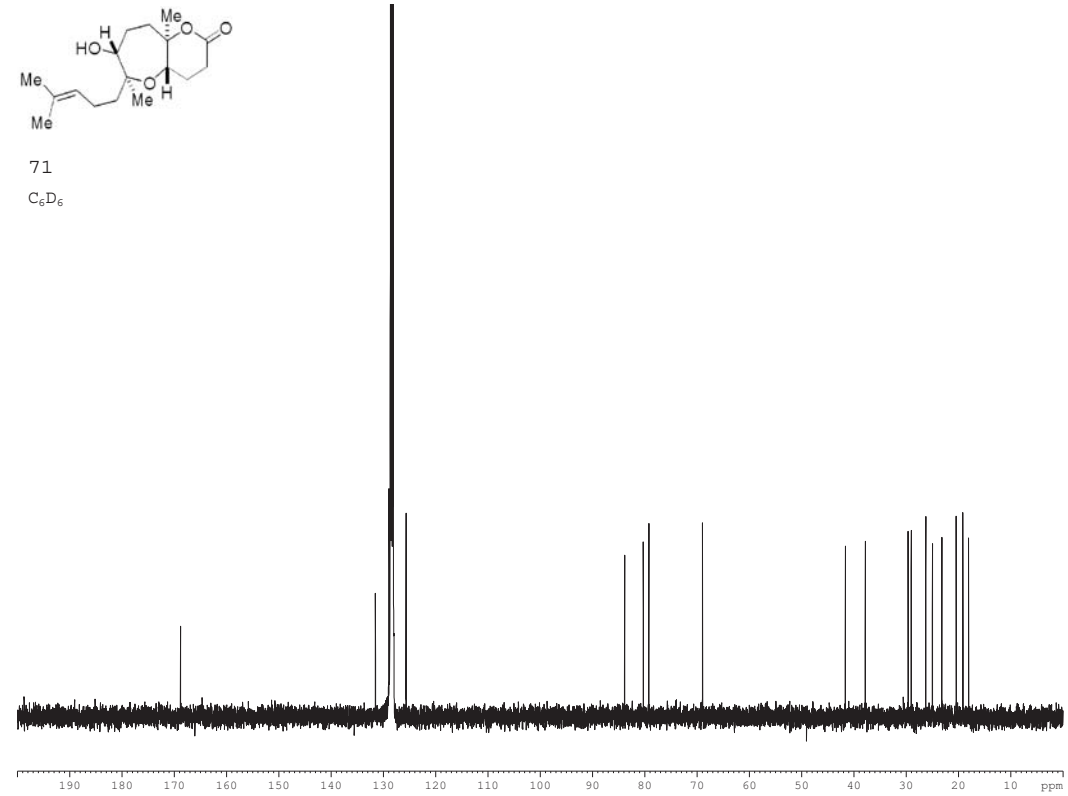

TIPSO
O
OAc
Me
Me
Me
C6D6
67
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.06
1.30
2.32
1.06
5.03
2.19
2.01
8.15
3.27
22.69


TIPSO
O
OAc
Me
Me
Me
C6D6
67
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


TIPSO
Me
Me
Me
Me
O
O
C6D6
69
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.00
1.05
0.99
2.18
3.34
3.36
28.02


TIPSO
Me
Me
Me
Me
O
O
C6D6
69
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


71
C6D6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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C6D6
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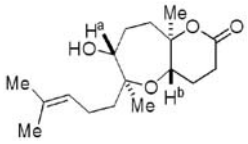

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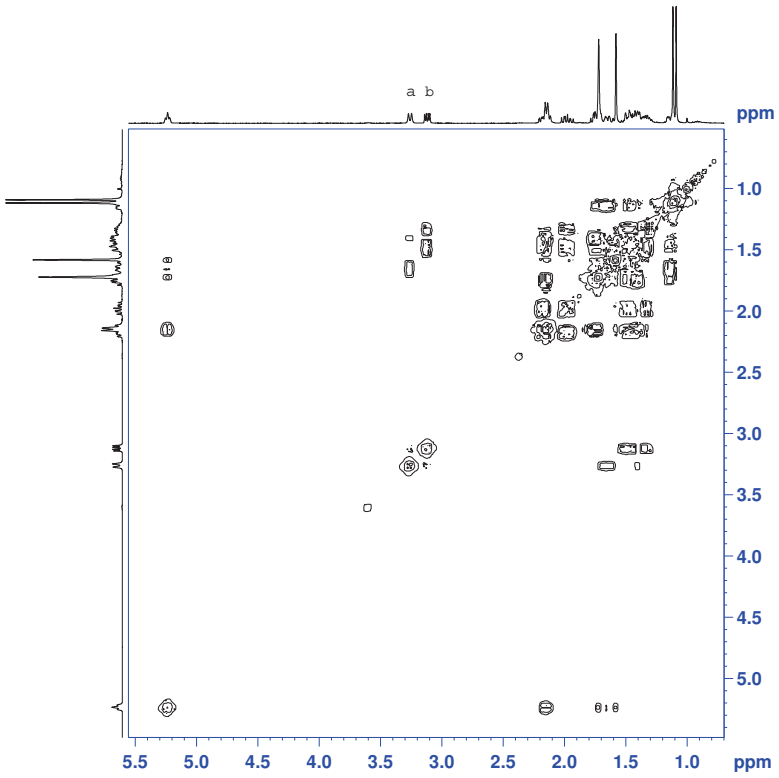
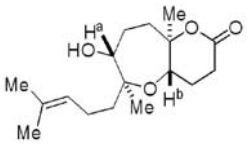
COSY





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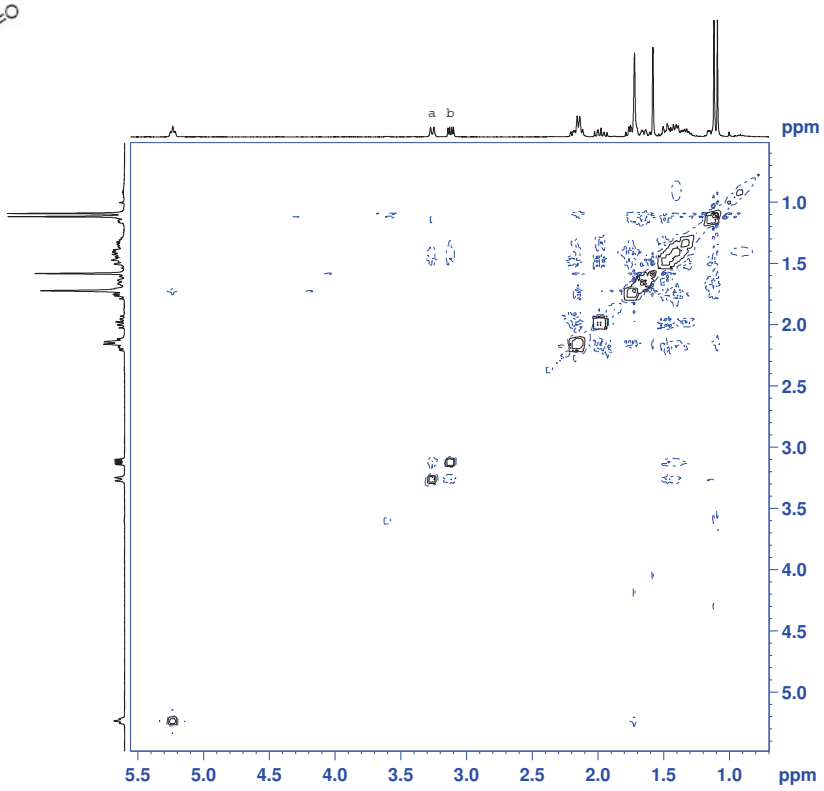

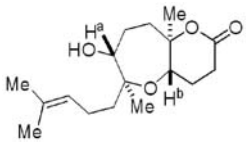

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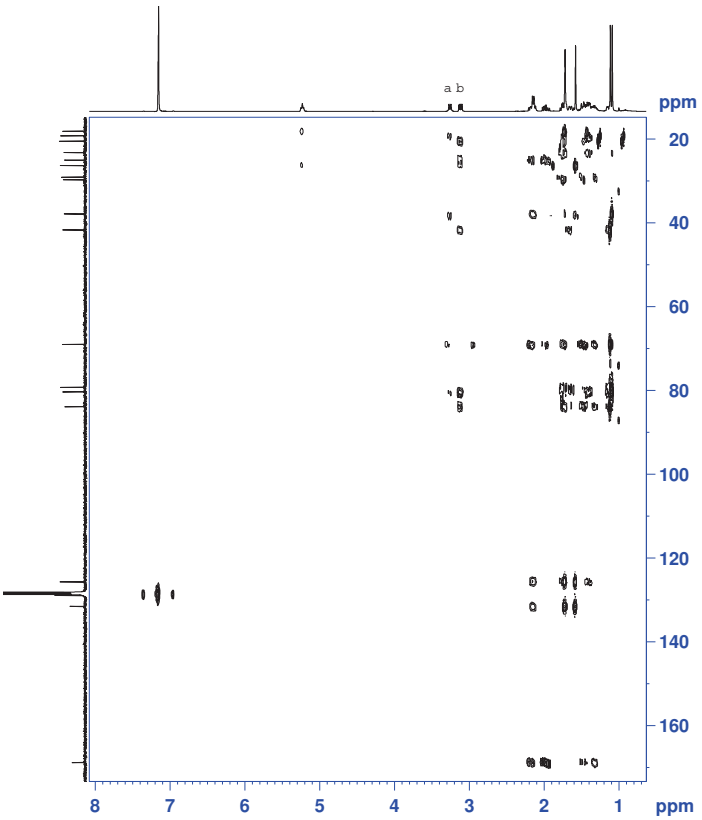

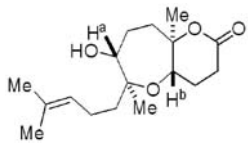

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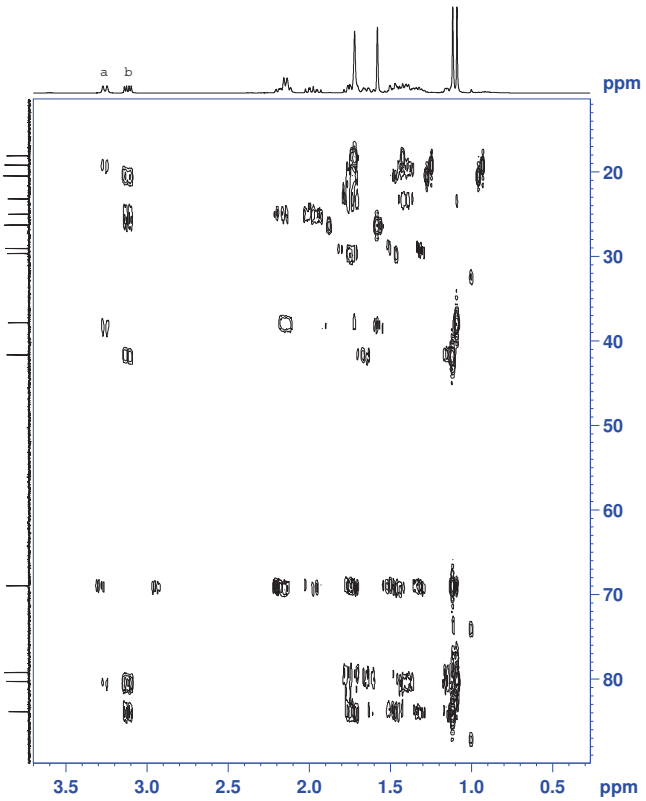

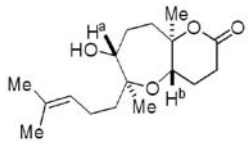

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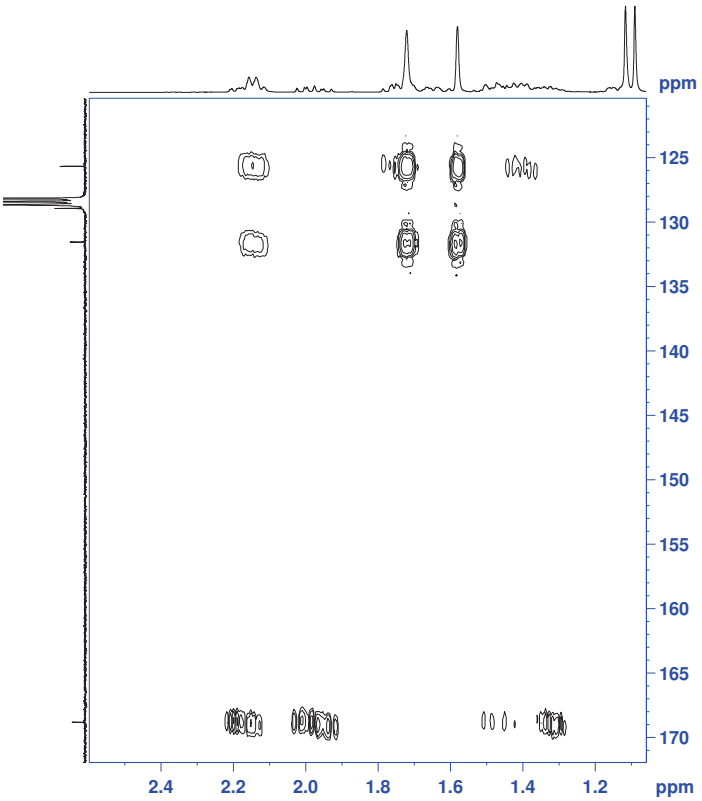

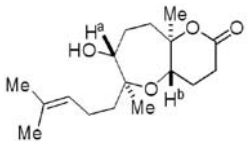

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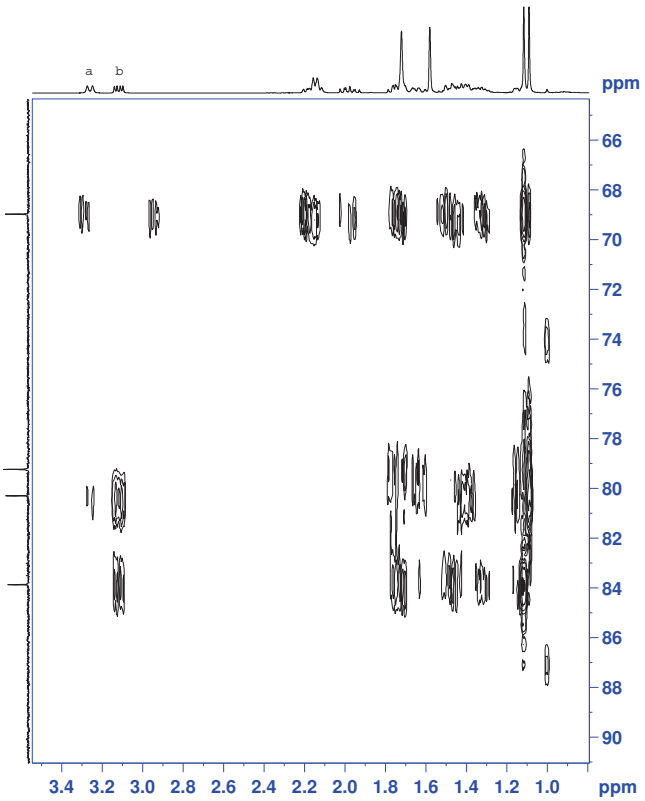

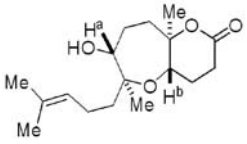

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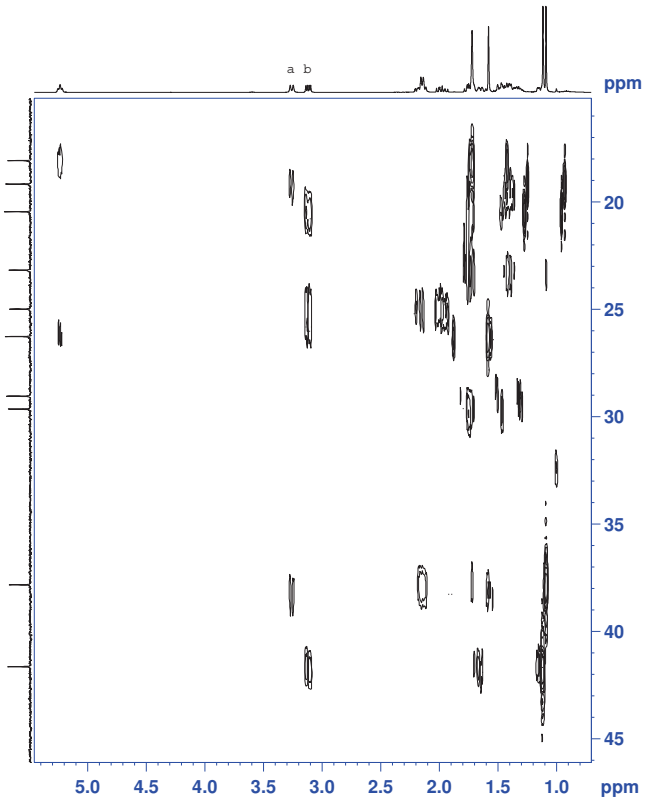

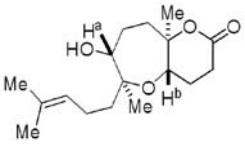

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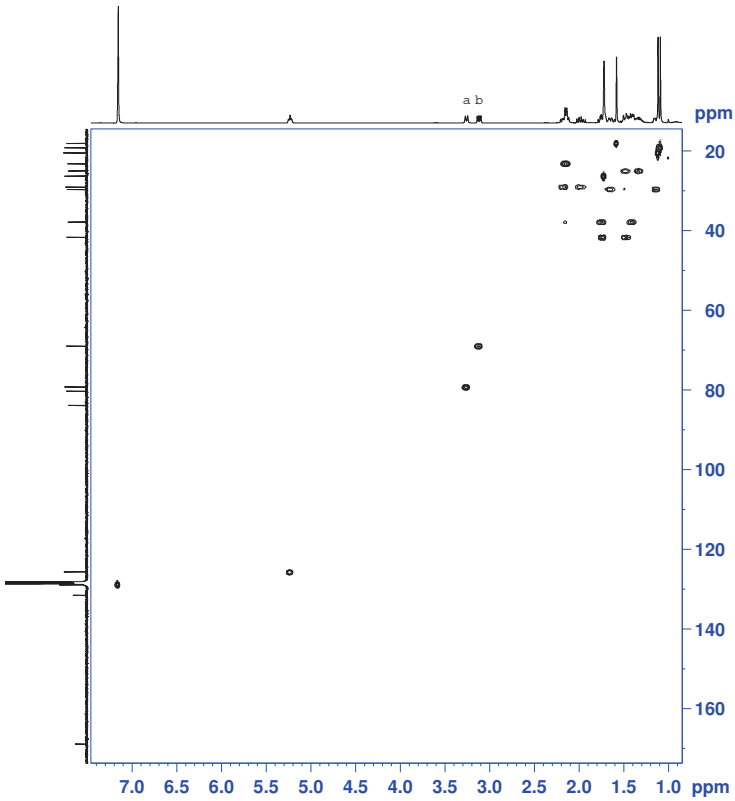
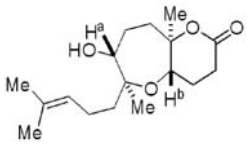
HSQC





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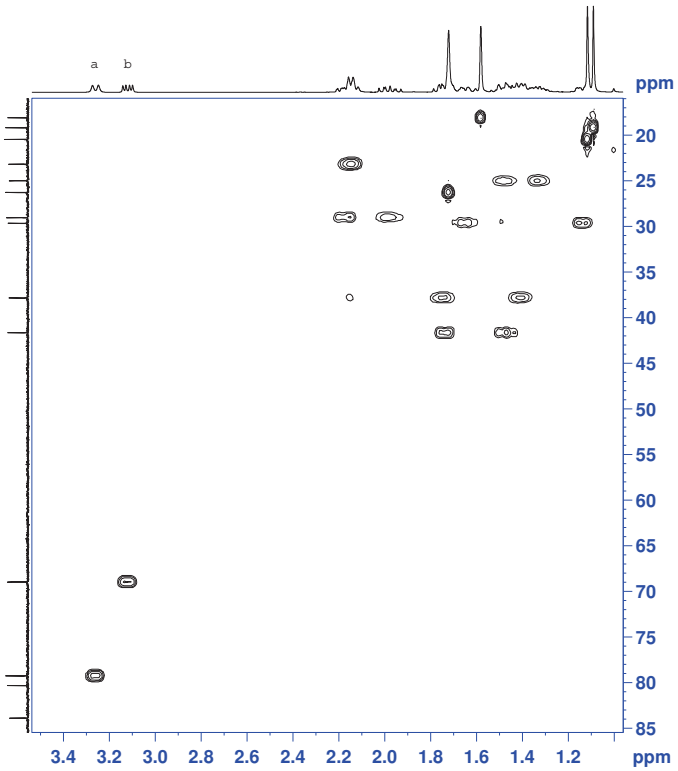
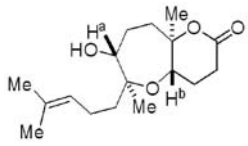
HSQC





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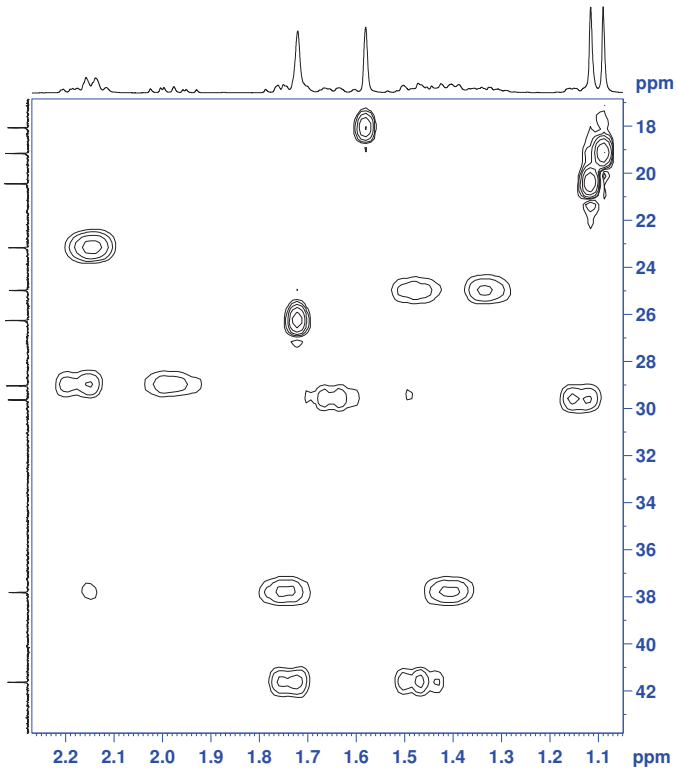
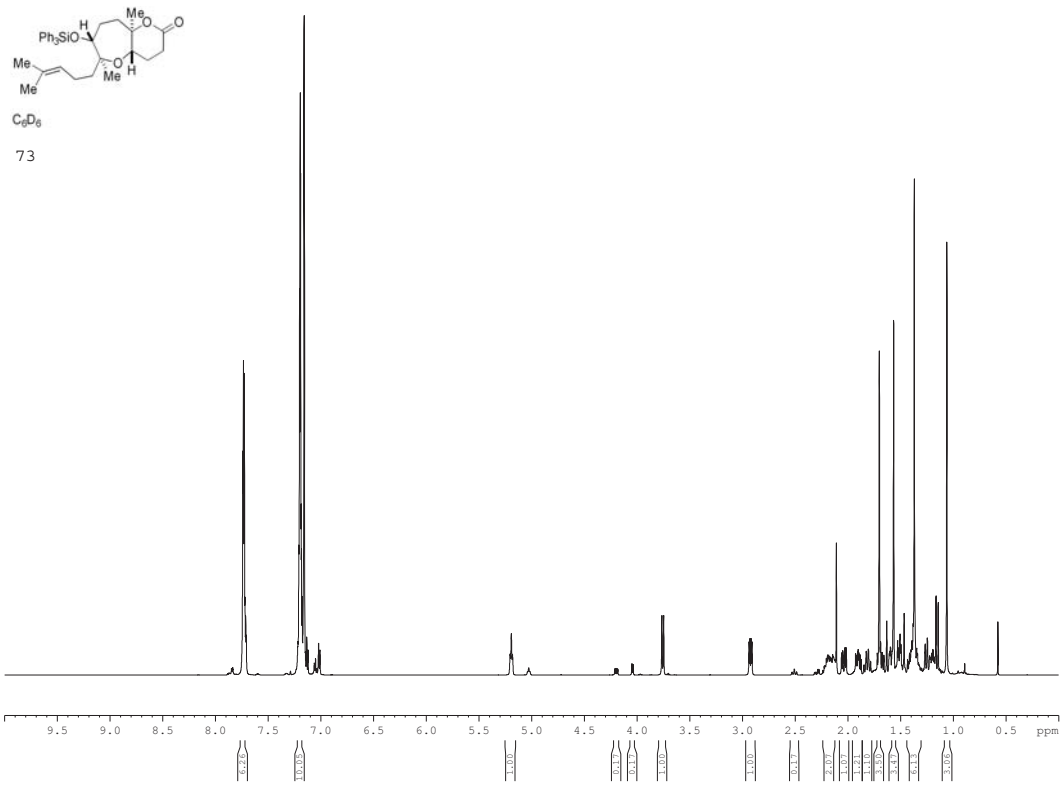
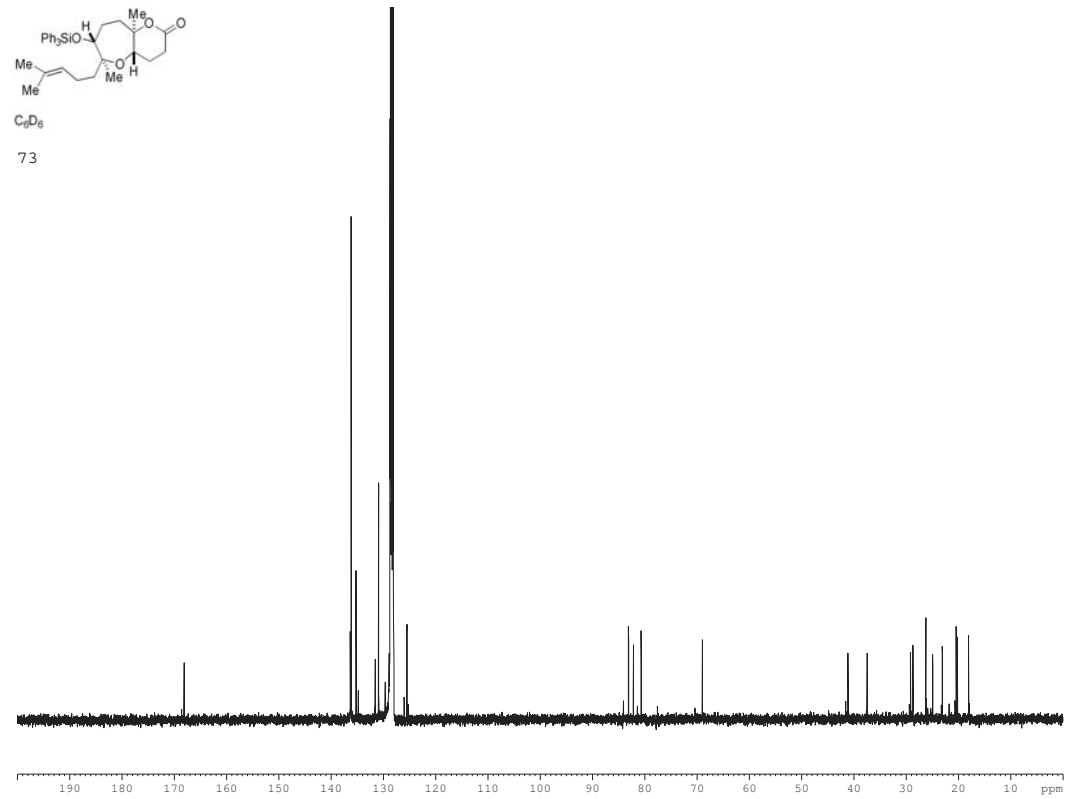



Me
Ph3SiO
H
O
O
Me
Me
Me
H
Me
C6D6
73
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
6.26
10.05
1.00
0.13
0.17
1.00
1.00
0.17
2.07
1.00
1.14
1.10
3.60
3.43
6.13
3.06


Me
Ph3SiO
H
O
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Me
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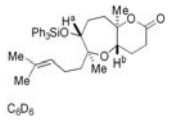
C6D6
73
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

SN081946 C6D6 gCOSY



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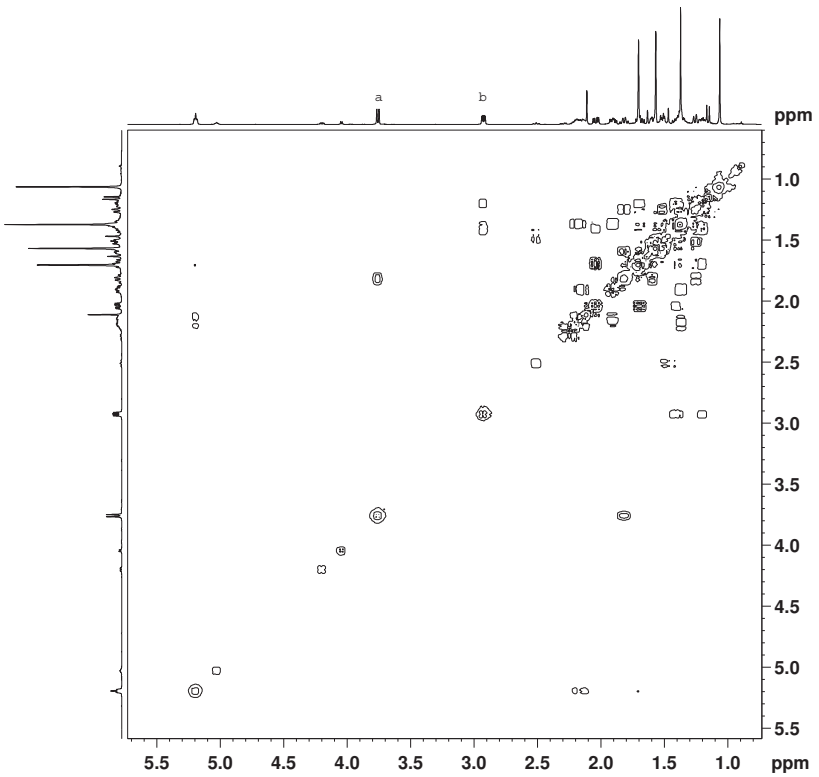
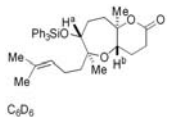


SN081946 C6D6 gNOSEY



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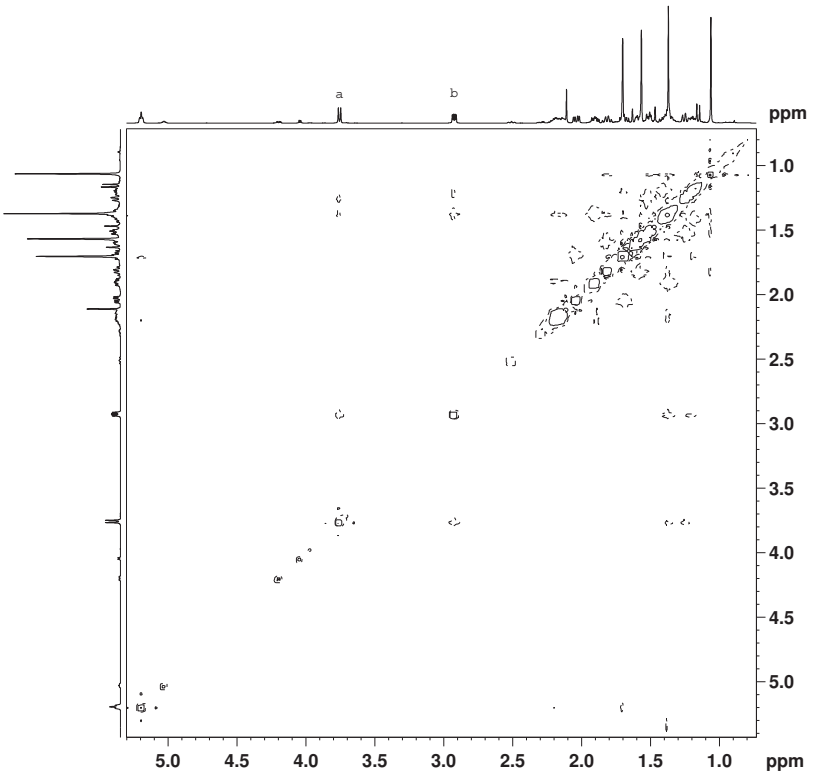

CURRICULUM VITAE

Sze-Sze Ng

Education

2003–present Massachusetts Institute of Technology
Pursuing Doctor of Philosophy in Chemistry
- Development of nickel-catalyzed carbon–carbon bond forming reactions under the supervision of Professor Timothy F. Jamison
- Synthetic studies toward *ent*-dioxepandehydrothyrsiferol

1999–2003 University of Texas at Austin
Bachelor of Science in Chemistry
- Graduation with honors in May 2003

Professional Experience

2003–present Massachusetts Institute of Technology
Research Assistant (Professor Timothy F. Jamison)
- Developed nickel-catalyzed, asymmetric reductive coupling of allenes and aldehydes via chirality transfer from chiral allenes
- Developed a new catalytic cycle for a nickel-catalyzed coupling of alkenes, aldehydes and silyl triflates
- Synthetic studies toward *ent*-dioxepandehydrothyrsiferol via epoxide-opening cascade

2001–2003 University of Texas at Austin
Undergraduate Research Fellow (Professor Michael J. Krische)
- Developed organocatalytic reactions

Undergraduate Teaching Assistant
- Led recitations of introductory organic chemistry classes

2001 Summer MD Anderson Cancer Center, Houston, TX
Undergraduate Research Intern (Professor Bimal K. Banik)
- Developed nitration of aromatic compounds on solid support

2000 Summer MD Anderson Cancer Center, Houston, TX
Undergraduate Research Intern (Professor Bimal K. Banik)
- Synthesized a tricyclic β-lactam via a Heck reaction

Awards

2007–2008 Massachusetts Institute of Technology
- Eli Lilly Graduate Fellowship, 2007–2008

2006–2007 Massachusetts Institute of Technology
- Bristol-Myers Squibb Graduate Fellowship, 2006–2007

2006–2007 Massachusetts Institute of Technology

- Roche Symposium - Excellence in Chemistry 2007
- MIT Wyeth Scholar Travel Grant 2007

Awards (continued from last page)

2003–2004 Massachusetts Institute of Technology

- Dean of Science Teaching Fellow, Spring 2003
- Award for Outstanding Teaching from Chemistry Education Office, 2003–2004

1999–2003 University of Texas at Austin

- University Honors, Fall 1999–May 2003
- Unrestricted Endowed Presidential Scholarship, 2001–2002
- Dorothy B. Banks Scholarship, 2002–2003
- Undergraduate Research Fellowship Award, 2001–2002 and 2002–2003

Publications

- Ng, S.-S.; Ho, C.-Y.; Jamison, T. F. "Nickel-catalyzed coupling of alkenes, aldehydes, and silyl triflates", *J. Am. Chem. Soc.* **2006**, *128*, 11513–11528.

- Ho, C.-Y.; Ng, S.-S.; Jamison, T. F. "Nickel-catalyzed, carbonyl-ene-type reactions: Selective for alpha olefins and more efficient with electron-rich aldehydes," *J. Am. Chem. Soc.* **2006**, *128*, 5362–5363.

- Ng, S.-S.; Jamison, T. F. "Nickel-catalyzed coupling of terminal allenes, aldehydes, and silanes," *Tetrahedron* **2006***, 62,* 11350–11359.

- Ng, S.-S.; Jamison, T. F. "Simple alkenes as substitutes for organometallic reagents: Nickel-catalyzed, intermolecular coupling of aldehydes, silyl triflates, and alpha olefins," *J. Am. Chem. Soc*. **2005**, *127*, 14194–14195.

    - Editor's Choice: Yeston, J. S. "The Value of a Nickel," *Science* **2005**, *309*, 2139.

- Ng, S.-S.; Jamison, T. F. "Enantioselective and regioselective nickel-catalyzed multicomponent coupling of chiral allenes, aromatic aldehydes, and silanes," *Tetrahedron* **2005**, *61*, 11405–11417.

- Ng, S.-S.; Jamison, T. F. "Highly enantioselective and regioselective nickel-catalyzed reductive coupling of allenes, aldehydes and silanes," *J. Am. Chem. Soc*. **2005**, *127*, 7320–7321.

- Wang, J.-C.; Ng, S.-S.; Krische, M. J. "Catalytic diastereoselective synthesis of diquinanes from acyclic precursors," *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683.

- Banik, B. K.; Samajdar, S.; Banik, I.; Ng, S.-S.; Hann, J. "Montmorillonite impregnated with bismuth nitrate: microwave-assisted facile nitration of β-lactams," *Heterocycles*, **2003**, *61*, 97–100.

- Ng, S.-S.; Banik, I.; Okawa, A.; Becker, F. F.; Banik, B. K. "Synthesis of tricyclic β-lactams via palladium acetate-induced Heck reaction," *J. Chem. Res., Synop.* **2001**, 118–119.

Presentations

May 2007 Bristol-Myers Squibb Chemistry Symposium, Lawrenceville, NJ

June 2007 Roche Symposium – Excellence in Chemistry, Nutley, NJ

July 2007 Organic Reactions and Processes Gordon Research Conference, Smithfield, RI (Poster)

Aug 2007 ACS National Meeting, Boston, MA

Mar 2008 Eli Lilly Grantee Symposium, Indianapolis, IN (Poster)